Antiparkinson's Agents

Therapeutic Class Review (TCR)

August 6, 2014

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to PSTCREditor@magellanhealth.com.

FDA-APPROVED INDICATIONS

Therapeutic Class	Drug	Manufacturer	Parkinson's Disease	Drug-induced EPS	RLS
Anticholinergics	benztropine[1]	generic	X	X except TD	
	trihexyphenidyl[2]	generic	X	X	
Dopa decarboxylase Inhibitor	carbidopa (Lodosyn®)[3]	generic	X (only as add on to levodopa/carbidopa)		
Dopamine precursor / dopa decarboxylase inhibitor	levodopa/carbidopa (Sinemet®, Sinemet® CR)[4]	generic	X		
	levodopa/carbidopa-oral disintegrating (ODT) (Parcopa™)[5]	generic	X		
MAO-B inhibitors	rasagiline (Azilect®)[6]	Teva Neuroscience	X		
	selegiline[7] (Eldepryl®)	generic	X (only as adjunct to levodopa/carbidopa)		
	selegiline – oral disintegrating (ODT) (Zelapar™)[8]	Valeant	X (only as adjunct to levodopa/carbidopa)		
Dopamine agonists	bromocriptine (Parlodel®)[9]	generic	X (only as adjunct to levodopa/carbidopa)		
	pramipexole (Mirapex®)[10]	generic	X		X
	pramipexole extended release (Mirapex® ER)[11]	Boehringer Ingelheim	X		
	ropinirole (Requip®)[12]	generic	X		X
	ropinirole extended release (ER) (Requip XL)[13]	generic	X		
	rotigotine (Neupro®)[14]	UCB	X		X
COMT inhibitors	entacapone (Comtan®)[15]	generic	X (only as adjunct to levodopa/carbidopa)		
	tolcapone (Tasmar®)[16]	Valeant	X (only as adjunct to levodopa/carbidopa)		
Dopamine precursor / dopa decarboxylase inhibitor / COMT inhibitor	levodopa/carbidopa/ entacapone (Stalevo®)[17]	generic	X		
Other (gabapentin prodrug)	gabapentin enacarbil (Horizant™)[18◊]	GlaxoSmithKline			X

EPS = extrapyramidal symptoms
RLS = restless legs syndrome
TD = tardive dyskinesia

◊Gabapentin enacarbil is also FDA-approved for postherpetic neuralgia (PHN). The PHN indication will not be reviewed here.
ŧRivastigmine (Exelon) will not be reviewed here due to a concurrent indication for Alzheimers.

In April 2008, Rotigotine (Neupro®) transdermal system was withdrawn from the market in the United States following discovery that rotigotine was prone to crystallization on the underside of the patch but reintroduced to the U.S. market post reformulation in July 2012.

OVERVIEW

Parkinsonism

Parkinson's disease (PD) is a progressive, neurodegenerative disorder with cardinal motor features of tremor, bradykinesia, and rigidity.[19] This disease affects more than 1.5 million Americans older than 50 years of age with the incidence increasing significantly with age.[20] The term "parkinsonism" describes the motor syndrome of bradykinesia, rigidity, tremor, and balance and gait problems.[21] Secondary parkinsonism, which has a different etiology and pathology than PD, is the predominant clinical manifestation of a number of disorders, including brain tumors near the basal ganglia, cerebral atherosclerosis, head trauma, and progressive supranuclear palsy.[22] Secondary parkinsonism can also be caused by toxins and drugs, especially antipsychotic agents.

Parkinson's disease and secondary parkinsonism are characterized by striatal dopamine deficiency. In PD, the degeneration of dopamine-containing neurons in the substantia nigra leads to the formation of Lewy bodies (intracellular neuronal inclusion bodies). While Lewy bodies are not present in secondary parkinsonism, the nigral striatal pathway may be impaired and nigral cell loss or loss of striatal cellular elements may occur.[23]

Despite advances in treatments over the years, there is no cure for PD. Symptomatic therapy can provide benefit for quite some time, but the continued, however slow, progression of PD eventually results in significant disability. Patients may not require treatment in the early stages of PD if symptoms do not cause functional impairment.[24] As the disease progresses, however, therapy becomes more complex, requiring dosage adjustments, incorporation of multiple medications, and the use of rescue treatments.[25] It is generally recommended that medication regimens be kept as simple as possible since the risk of adverse effects is generally lower when fewer agents are used at higher doses than when multiple drugs are used at lower doses.[26]

Anticholinergics were the first medications indicated for the treatment of PD. Anticholinergics such as benztropine and trihexyphenidyl improve motor symptoms in some patients with PD, especially younger patients with resting tremor as a predominant symptom. Today, they are used primarily as adjuncts to levodopa treatment and as treatments for tremor symptoms. These drugs often cause side effects in the elderly and are contraindicated in patients with glaucoma, benign prostatic hypertrophy, and dementia.[27,28]

A major breakthrough in the treatment of PD was the replacement of dopamine in the brain by using levodopa (exogenous dopamine does not cross the blood-brain barrier). Combination of levodopa with carbidopa, a peripheral dopa decarboxylase inhibitor that does not cross the blood-brain barrier, led to an increase in the amount of levodopa available to the brain for conversion to dopamine and a reduction in the incidence of nausea and vomiting.[29] Although levodopa provides benefit to nearly all PD patients, long-term treatment with levodopa is complicated by the development of motor fluctuations, dyskinesias, and neuropsychiatric complications.[30,31,32,33] Patients may experience a

"wearing-off" effect characterized by a shorter duration of benefit from each levodopa dose, causing parkinsonian symptoms to reemerge. Patients can also experience an "on-off" effect characterized by unpredictable, abrupt fluctuations in motor state from when the medication is effective and symptoms are controlled ("on") to when parkinsonian symptoms worsen ("off"). Additionally, as PD progresses, patients develop symptoms that do not respond well to levodopa therapy, including freezing episodes, autonomic dysfunction, falling, and dementia.

Monoamine oxidase B inhibitors (MAO-Bs) are naturally generated enzymes predominantly located in the brain that breaks down several chemicals, including dopamine. Since MAO-Bs are abundant in the striatum and involved in dopamine metabolism, the theory is that MAO-Bs inhibition will increase the quantity of dopamine available and result in the reduction of some of the motor symptoms seen with PD.[34] Rasagiline (Azilect) and selegiline (generic, Zelapar), highly selective inhibitors of monoamine oxidase (MAO) B, have been shown to cause a slight improvement in motor performance upon initiation of therapy and to delay the development of disability that requires the addition of levodopa. Rasagiline is three times more potent than selegiline. Although their effectiveness as neuroprotective agents has yet to be demonstrated by clinical trials, the MAO-B inhibitors are effective as adjuncts to allow lower doses of levodopa while lengthening dosage intervals. Both agents are approved for use as adjunct to levodopa in later stage disease because they can increase the percent of "on" time in advanced PD patients. Rasagiline is also approved for use as monotherapy in early PD as well as an adjunct to patients receiving dopamine agonists.

Dopamine agonists [bromocriptine (Parlodel), pramipexole (Mirapex, Mirapex ER), ropinirole (Requip, Requip XL), and rotigotine (Neupro)] are used in early PD. These agents have a levodopa-sparing effect and can reduce the frequency of "off" time. While monotherapy with dopamine agonists has been shown to reduce the subsequent dyskinesias and other motor complications in comparison to levodopa, monotherapy has the potential to cause orthostatic hypotension and neuropsychiatric adverse effects, such as confusion and hallucinations.[35] Because of this, these agents should be avoided in patients with confusion or memory or cognitive impairment, as well as in those at risk of hypotension.[36,37] Apomorphine (Apokyn®), an injectable, non-ergot dopamine agonist, has been approved for the treatment of hypomobility in advanced PD. Since it is an injectable product, it will not be considered in this review.

The addition of catechol-O-methyltransferase (COMT) inhibitors, entacapone (Comtan) and tolcapone (Tasmar), reduces the end-of-dose failure ("wearing off") of levodopa therapy that causes motor complications. By reducing the peripheral metabolism of levodopa, COMT inhibitors allow for the use of lower doses of levodopa and are both approved as adjunct to levodopa therapy.[38] Some experts recommend the initiation of a COMT inhibitor at the onset of levodopa therapy to reduce the risk of developing motor complications.

The 2006 guidelines from the American Academy of Neurology (AAN) recommended that entacapone be offered to patients with PD with motor fluctuations to reduce off time.[39] Pramipexole, ropinirole, and tolcapone are recommended as alternatives to be considered, although the AAN notes that tolcapone, due to hepatotoxicity, should be used with caution and requires monitoring. For patients who continue to experience unpredictable on and off periods, a MAO-B inhibitor or amantadine may be added to the patient's drug regimen. There is insufficient evidence to conclude that any one agent is superior to another in reducing off time.

An evidence-based review reported in 2005 by the Movement Disorder Society ranked the efficacy of the various treatments based on placebo-controlled trials of patients with PD between 2001 and 2004.[40] In the review, levodopa, the MAO-B inhibitors, and the dopamine agonists are all rated as efficacious monotherapy in patients with early PD. The anticholinergics, as well as amantadine and bromocriptine, are rated as likely efficacious, and the COMT inhibitors are rated non-efficacious in this patient group. In patients with more severe disease, the COMT inhibitors, the dopamine agonists (with the exception of ropinirole), bromocriptine, and apomorphine (Apokyn) are all rated as efficacious adjunct therapy to levodopa. The anticholinergics and amantadine are rated as likely efficacious. The group cites insufficient evidence to rate the efficacy of the MAO-B inhibitors and ropinirole in this patient group.

Restless Legs Syndrome

Restless Legs Syndrome (RLS) is a neurological sensory disorder in which patients experience irrepressible sensations in the legs or arms while sitting or lying still to cause them to move their arm or legs. Providers will need to rule out other movement disorders with similar symptoms to RLS like periodic limb movement disorder (PLMD), antipsychotic adverse effects, and dyskinesis to correctly medicate. Studies suggest that RLS is associated with the dopamine system and depletion of iron stores.[41] Historically, RLS has been treated with opioids, benzodiazepines, anticonvulsants (including the immediate-release formulation of gabapentin), iron replacement (in patients with low serum ferritin levels), and dopaminergic agents (e.g., carbidopa/levodopa). Prior to 2000, levodopa was the dopaminergic agent most studied for RLS. Pramipexole (Mirapex), ropinirole (Requip), and rotigotine (Neupro) are approved for an indication of RLS and there has been increased focus on the use of dopamine agonists in the treatment of this disorder. Gabapentin enacarbil (Horizant) is also FDA-approved for RLS.

When nonpharmacologic modifications like sleep hygiene, avoiding medications that provoke RLS, and lifestyle adjustments are ineffective, pharmacologic therapies should be added.[42] The American Journal of Medicine 2007 RLS guidelines report that dopaminergic therapy appears to be the most effective and relieves symptoms rapidly.[43] Depending on the type of RLS, an algorithm by an expert panel recommends the non-ergot dopamine agonists pramipexole and ropinirole as drugs of choice.[44] Rotigotine (Neupro) is also a non-ergot dopamine agonist. Levodopa or levodopa/carbidopa is recommended for intermittent RLS. Gabapentin or gabapentin enacarbil are alternatives.

The 2012 American Academy of Sleep Medicine (AASM) RLS practice parameters recommend pramipexole (Mirapex) and ropinirole (Requip) for RLS.[45] Gabapentin enacarbil (Horizant) is also recommended but conservatively since relatively new. Levodopa with dopa decarboxylase inhibitor is recommended but for patients with intermittent RLS who do not require daily therapy for RLS. Cabergoline is only recommended if first-line agents are not an option. Carbamazepine, gabapentin, pregabalin, clonidine, and for patients with low ferritin levels, iron supplementation, are listed as options, however evidence to support their use in RLS is limited. The guidelines note that rotigotine (Neupro) is effective in the treatment of moderate to severe RLS, but the patch was off the market at the time of guideline update.

Early trials indicated that gabapentin may provide effective treatment for RLS.[46,47] Gabapentin absorption occurs through active transport by low-capacity nutrient transporter expressed in a narrow region of the upper small intestine. As a result, gabapentin bioavailability decreases with increasing dose as well as plasma exposure to gabapentin is variable among patients.[48] Additionally, the short

half-life of gabapentin requires frequent dosing. Gabapentin enacarbil (Horizant) is an actively transported prodrug of gabapentin through absorption by high-capacity nutrient transporters located throughout the large and small intestine. After absorption, gabapentin enacarbil is converted to gabapentin by carboxylesterases. Gabapentin enacarbil is an extended-release tablet and dosed once daily. Gabapentin is not interchangeable with gabapentin enacarbil.

PHARMACOLOGY[49]

Therapeutic Class	Drug	Mechanism of Action
Anticholinergics	benztropine trihexyphenidyl	▪ Suppress central cholinergic activity ▪ Inhibit the reuptake and storage of dopamine at central dopamine receptors, thereby prolonging the action of dopamine
Dopamine precursor / dopa decarboxylase inhibitor	levodopa / carbidopa (Sinemet, Sinemet CR, Parcopa)	▪ Levodopa is the immediate precursor to dopamine ▪ Carbidopa inhibits L-amino-acid-decarboxylase (L-AAD) and prevents the decarboxylation of levodopa
MAO-B inhibitors	rasagiline (Azilect) selegiline selegiline (Zelapar)	▪ Select irreversible inhibitors of monoamine oxidase type B activity ▪ Block dopamine breakdown ▪ Increase dopaminergic activity ▪ Interfere with dopamine reuptake at the synapse
Dopamine agonists	bromocriptine (Parlodel) pramipexole (Mirapex, Mirapex ER) ropinirole (Requip, Requip XL)	▪ Directly stimulate the dopamine receptors in the corpus striatum
	rotigotine (Neupro)	▪ Non-ergoline dopamine agonist that binds to the D2 dopamine receptor within the caudate-putamen
COMT inhibitors	entacapone (Comtan) tolcapone (Tasmar)	▪ Inhibit COMT (catechol-O-methyltransferase) ▪ Prevent peripheral conversion of levodopa to 3-O-methyldopa (3OMD) ▪ Increase plasma levodopa levels
Dopamine precursor / dopa decarboxylase inhibitor / COMT inhibitor	levodopa / carbidopa / entacapone (Stalevo)	▪ Levodopa is the immediate precursor to dopamine ▪ Carbidopa inhibits L-AAD and prevents the decarboxylation of levodopa ▪ Entacapone inhibits COMT and increases plasma levodopa levels
Gabapentin prodrug	gabapentin enacarbil (Horizant)	▪ Precise mechanism unknown in RLS. ▪ In vitro studies show that gabapentin binds to voltage activated calcium channels

Gabapentin does not exhibit affinity for benzodiazepine, opiate (mu, delta, or kappa), or cannabinoid 1 receptor sites. The dependence and abuse potential of gabapentin has not been evaluated in human studies.

PHARMACOKINETICS[50]

Drug	Bioavailability (%)	Half-Life (hr)	Metabolism	Excretion (%)
Anticholinergics				
benztropine[51]	--	--	CYP3A and hydroxylation	Urine: 6
trihexyphenidyl[52]	--	--	Metabolites	Urine
Dopamine precursor / dopa decarboxylase inhibitor				
levodopa/carbidopa (Sinemet, Parcopa)[53,54]	--	1.5	Extensive	Urine
MAO-B inhibitors				
rasagiline (Azilect)[55]	36	3	CYP1A2	Urine: 62 Feces: 7
selegiline[56]	--	10	Three active metabolites	Urine: 45
selegiline (Zelapar)[57]	greater than conventional selegiline tablets	10	Three active metabolites – concentrations reduced 3- to 10-fold compared to conventional selegiline tablets	
Dopamine agonists				
bromocriptine (Parlodel)[58]	28	15	CYP3A	Urine: 6
pramipexole (Mirapex)[59]	>90	8 (young) 12 (elderly)	Unchanged	Urine: 90
pramipexole ER (Mirapex ER)[60]	>90	8.5 (young) 12 (elderly)	Unchanged	Urine: 90
ropinirole (Requip)[61]	55	6	CYP1A2	Urine: >88
ropinirole ER (Requip XL)[62]	45-55	6	CYP1A2	Urine: >88
rotigotine (Neupro)[63]	1 -46 (varies based on patch location	5-7	Multiple metabolic process to include conjugation, N-dealkylation and sulfate conjugation, and glucuronidation	Urine: 71 Feces: 23
COMT inhibitors				
entacapone (Comtan)[64]	35	2.4	isomerization to CIS-isomer and direct glucuronidation of parent and CIS-isomer to inactive conjugate	Urine: 10 Feces: 90
tolcapone (Tasmar)[65]	65	2-3	glucuronidation to inactive conjugate	Urine: 60 Feces: 40
Gabapentin prodrug				
gabapentin enacarbil (Horizant)[66]	75	5.1-6	extensive first pass hydrolysis	Urine

The pharmacokinetics for levodopa/carbidopa/entacapone (Stalevo) is similar to the individual components of the drug.[67]

CONTRAINDICATIONS/WARNINGS[68,69,70,71,72,73,74,75,76,77,78,79,80, 81]

A boxed warning appears in the tolcapone (Tasmar) prescribing information. Three fatal cases of acute, fulminant liver failure have been reported in the first six months of therapy. Patients must sign an informed consent to start therapy with tolcapone. The warning states that "the actual incidence of hepatocellular injury appears to be ten- to 100-fold higher than the background incidence in the general population. Prior to therapy initiation, the patient should have no clinical evidence of liver disease or hepatic lab values greater than normal. If patients do not respond to tolcapone in three weeks, therapy should be stopped.

Concomitant use of non-selective MAO inhibitors with levodopa/carbidopa (Parcopa, Sinemet, Sinemet CR) can result in hypertensive crisis; simultaneous use of these agents is contraindicated. The MAOI must be discontinued two weeks prior to starting levodopa/carbidopa. Levodopa/carbidopa is also contraindicated in patients with narrow-angle glaucoma.

The anticholinergics, benztropine and trihexyphenidyl, should not be given to patients with narrow angle glaucoma. Benztropine should be used cautiously in patients with benign prostatic hypertrophy because it can exacerbate urinary retention. In addition, the manufacturer considers prostatism, dementia, and tardive dyskinesia contraindicated to the use of this drug. These agents were added to the Beers Criteria list for potentially inappropriate medication use in older adults in 2012.[82]

Due to potentially fatal reactions that have occurred in patients receiving MAO inhibitors concomitantly with meperidine, the use of rasagiline (Azilect) and selegiline (generic, Zelapar) with meperidine is contraindicated. For similar reasons, these two drugs should not be used concurrently with methadone, propoxyphene, or tramadol; and this contraindication is often extended to other opioids. Rasagiline is also contraindicated with the concurrent use of dextromethorphan, St. John's wort, or cyclobenzaprine. Rasagiline and selegiline are contraindicated for use with sympathomimetic amines due to the potential for severe hypertensive reactions. Other contraindications for the MAO-B inhibitors are general anesthesia, pheochromocytoma, and concurrent use with other MAO inhibitors. Concomitant use of MAO-B inhibitors with non-selective MAO inhibitors, SNRIs, SSRIs or tricyclic antidepressants is not recommended.

Case reports of patients falling asleep during activities of daily living, including while operating a motor vehicle, have been reported with dopamine agonists. Prescribers should monitor patients for somnolence and drowsiness; however, prescribers should be aware some patients indicated they had no warning signs prior to the event. Class warning language has been added to all agents regarding these "sleep attacks" due to their central dopaminergic activity.

Use of bromocriptine (Parlodel) is contraindicated if the patient has experienced hypersensitivity to bromocriptine, has uncontrolled hypertension, or has sensitivity to ergot alkaloids. Bromocriptine should be discontinued if the patient becomes pregnant; discontinuation should be considered if the patient has plans to become pregnant. Adverse effects during pregnancy, such as preeclampsia, eclampsia, or pregnancy-induced hypertension have been known to occur. Bromocriptine should be avoided in post-partum patients with a history of coronary cardiovascular disease or other severe cardiovascular condition unless withdrawal is considered medically contraindicated. Pramipexole (Mirapex, Mirapex ER), ropinirole (Requip, Requip XL), and rotigotine (Neupro) have a warning in the prescribing information regarding the potential for falling asleep during activities of daily living, and patients should be informed of this risk prior to starting treatment. Other factors such as sedating

medications, drug interactions increasing the exposure to these drugs, and sleep disorders can increase the risk of excessive drowsiness or falling asleep. In addition, dopaminergic agonists tend to impair the regulation of blood pressure and can cause symptomatic hypotension and impaired capacity to respond to postural changes. Therefore careful monitoring during dose escalation and informed risk is needed.

In September 2012, the FDA warned of the possibility of an increased risk of new onset heart failure in individuals using pramipexole. Current data is not conclusive at this point and further safety evaluation is underway.[83] The warning of new onset heart failure is not in pramipexole's label.

Rotigotine (Neupro) contains sodium metabisulfate and contains a warning for those allergic to sulfites. Sulfites can result in allergic-type anaphylactic symptoms. Asthmatics may be more prone to sulfite sensitivities. Hallucinations or psychotic-like behavior, and dyskinesia may occur.

In a meta-analysis, pramipexole and ropinirole were compared for the risk of somnolence.[84] The pooled, relative risk of somnolence was 4.98 compared to the placebo group based on four trials. In a comparison between patients taking levodopa and pramipexole or ropinirole, the pooled, relative risk was 2.06.

Reports have associated ropinirole with a symptom complex that resembles neuroleptic malignant syndrome with no other obvious etiology linked to rapid dose reduction and withdrawal, rapid titration, and any changes in dopaminergic therapy. Therefore, the dose should be titrated down slowly over a seven-day period to prevent this withdrawal.

In 2009, warnings were added to the labeling of many of the antiparkinson's agents regarding intense urges to gamble, increased sexual urges, and other intense urges and the inability to control these urges while taking drugs that increase central dopaminergic tone. A cause-effect relationship has not been proven, although some urges were reported to have stopped in some cases when the dose was reduced or the medication was stopped.

In August 2010, the FDA notified healthcare professionals about concerns that the use of levodopa/carbidopa/entacapone may be associated with an increased risk of cardiovascular events, including heart attack, stroke, and cardiovascular death, when compared to the use of carbidopa/levodopa. Based on findings from the Stalevo Reduction In Dyskinesia Evaluation – Parkinson's Disease (STRIDE-PD) trial, which reported an imbalance in the number of myocardial infarctions in patients treated with levodopa/carbidopa/entacapone compared to those receiving only carbidopa/levodopa, the FDA has announced the intent to conduct a meta-analysis to validate these findings. Previous clinical trials with levodopa/carbidopa/entacapone have not shown an imbalance in myocardial infarction, stroke, and cardiovascular death. Until additional data are available, the cardiovascular status of patients taking levodopa/carbidopa/entacapone should be evaluated regularly, especially if there is a history of cardiovascular disease.

Epidemiological studies have shown that patients with PD have a higher risk (two- to approximately six-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to PD or other factors, such as drugs used to treat PD, is unclear. For the reasons stated above, patients and providers are advised to monitor for melanomas frequently and on a regular basis when using entacapone-containing products for any indication. Ideally, periodic skin examination should be performed by appropriately qualified individuals (e.g., dermatologists).

In June 2011, the FDA notified the public to medication error reports in which patients were given risperidone (Risperdal) instead of ropinirole (Requip®) and vice versa.[85] FDA evaluated 226 wrong drug medication errors relating to confusion between risperidone and ropinirole obtained from FDA's Adverse Event Reporting System database and the Institute for Safe Medication Practices. In some cases, patients who took the wrong medication needed to be hospitalized. The FDA determined that the factors contributing to the confusion between the two products include: similarities of both the brand (proprietary) and generic (established) names; similarities of the container labels and carton packaging; illegible handwriting on prescriptions; and overlapping product characteristics, such as the drug strengths, dosage forms, and dosing intervals.

There are no specific contraindications to the use of gabapentin enacarbil (Horizant) listed in the product information. Gabapentin enacarbil may cause somnolence/sedation and dizziness; therefore, patients should become experienced with the way gabapentin enacarbil may affect them specifically before operating a motor vehicle or other heavy machinery. Gabapentin enacarbil is not recommended for patients who are required to sleep during the daytime and remain awake at night. Due to differing pharmacokinetic profiles, gabapentin enacarbil is not interchangeable with other gabapentin products. The safety and effectiveness of gabapentin enacarbil have not been studied in patients with epilepsy. Gabapentin enacarbil is a prodrug of the anticonvulsant gabapentin; therefore, patients taking gabapentin enacarbil should also be monitored for a potential increased risk of suicidal thoughts and behavior.

DRUG INTERACTIONS[86,87,88,89]

Many different drug interactions occur with the antiparkinsonian agents. Drug interaction references should be reviewed when prescribing concomitant medications. Drugs that may antagonize dopamine agonists are phenothiazines, haloperidol, metoclopramide, and butyrophenones and diminish the effectiveness of the dopamine agonists. In addition, dopamine agonists should be used with caution with alcohol and other central nervous system (CNS) depressants. Use of levodopa/carbidopa in combination with dopamine-depleting agents, such as reserpine or tetrabenazine is not recommended.

Pramipexole (Mirapex, Mirapex ER) levels may be increased by renally-excreted basic drugs (e.g., cimetidine, verapamil, and quinidine).

Ropinirole (Requip, Requip XL) may be potentiated by CYP1A2 inhibitors, such as ciprofloxacin.

Because gabapentin enacarbil is not a substrate, inhibitor or inducer of any major cytochrome P450 enzymes or substrate or inhibitor of P-glycoprotein *in vitro*, no clinically relevant drug-to-drug interactions is expected.

ADVERSE EFFECTS

Anticholinergics[90]

Adverse effects of anticholinergic drugs are common and often limit their use. The most common CNS effects include memory impairment, acute confusion, hallucinations, sedation, and dysphoria. Peripheral anticholinergic adverse effects include dry mouth, blurred vision, constipation, nausea, urinary retention, impaired sweating, and tachycardia.

levodopa/carbidopa (Parcopa, Sinemet, Sinemet CR)[91]

The most frequently reported adverse effects with levodopa are adventitious movements, such as choreiform or dystonic movements (10 to 90 percent), anorexia (50 percent), nausea/vomiting with or without abdominal pain and distress (80 percent), dry mouth, dysphagia, dysgeusia (4.5 to 22 percent), sialorrhea, ataxia, increased hand tremor, headache, dizziness, numbness, weakness/faintness, confusion, insomnia, hallucinations, delusions, agitation, and anxiety.

Dopamine Agonists

Drug	Confusion	Constipation	Dizziness	Dyskinesia	Hallucinations	Nausea
bromocriptine (Parlodel)[92]	reported	reported	reported	reported	reported	reported
pramipexole (Mirapex)[93]	4-10 (1-7)	10-14 (6-9)	25-26 (24-25)	47 (31)	9-17 (3-4)	28 (18)
pramipexole ER (Mirapex ER)[94]	nr	14 (2)	12 (7)	17 (8)	5 (1)	22 (9)
ropinirole (Requip)[95]	5-9 (1)	6 (nr)	40 (22)	>1	>5	60 (22)
ropinirole ER (Requip XL)[96]	nr	4 (2)	6-8 (3)	13 (3)	8 (2)	11-19 (4)
rotigotine (Neupro)[97]	nr*	nr* 5-9ŧ (19)	20-21 (11)* nrŧ	nr* 14-17ŧ (7)	nr* 7-14ŧ (3)	34-41 (13)* 22-28ŧ (19)

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. Incidences for the placebo group are indicated in parentheses. nr = not reported.*Early –stage PD in 6 mg/24 hour group. ŧAdvanced-stage PD at 8 mg/24h and 12 mg/24h.

As rotigotine is a patch, application site reactions do occur. The adverse effect ranges from 15 percent in early stage PD to 23 percent in advanced-stage PD. Rotating the patch location may decrease the reaction. Dopamine agonists can cause peripheral edema and its associative weight gain. Patients more sensitive to fluid retention like congestive heart failure and renal insufficiency should be monitored.

Dopamine agonists appear to impair the systemic regulation of blood pressure resulting in orthostatic hypotension during dose escalation. Patient's with PD appear to have a decreased response to orthostatic challenge and monitoring of orthostatic hypotension is recommended.[98] Other precautions include a 9 percent increase in hallucinations, 6 percent increase risk of somnolence, and a potentiation of dopaminergic effects that may result in exacerbating dyskinesia. A human data study did not show statistical changes between treatment arms in retinal pathology but the animal data study in albino rats showed some retinal degeneration.[99]

There is growing evidence that dopamine agonists are associated with disorders of impulse control, including pathologic shopping, gambling, and hypersexuality. In a retrospective analysis, the lifetime prevalence for these behaviors in patients with PD was 6.1 percent. This risk increased to 13.7 percent among those on dopamine agonists.[100] Risk factors for these disorders were younger age at PD onset ($p=0.006$), high novelty-seeking traits ($p<0.001$), medication-induced hypomania or mania ($p=0.001$), impaired planning ($p=0.002$), or personal or immediate family history of alcohol abuse ($p<0.05$).[101]

COMT Inhibitors

Drug	Anorexia	Diarrhea	Dyskinesia	Hallucinations	Orthostatic complaints	Nausea	Somnolence
entacapone (Comtan)[102]	nr	8-20 (7)	13-25 (11)	4-9	13 (14)	10-20 (12)	4-8 (10)
tolcapone (Tasmar)[103]	19-23 (13)	16-34 (8)	42-51 (20)	24	17-24 (14)	28-50 (18)	16-32

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. Incidences for the placebo group are indicated in parentheses. nr = not reported.

Rare cases of fatal hepatotoxicity have been reported with tolcapone (Tasmar), leading to a recommendation of more stringent liver function monitoring.[104] In the 2000 Practice Parameters, The Quality Standards Subcommittee of the American Academy of Neurology recommends that tolcapone should only be used in PD patients taking levodopa who are experiencing symptom fluctuations and are not responding satisfactorily to or are not appropriate candidates for other adjunctive therapy. The Practice Parameters recommend that liver function monitoring should be done per the product labeling: baseline and then periodically (e.g., every two to four weeks) for the first six months and thereafter as clinically necessary. Tolcapone should be discontinued if alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increase to more than twice the upper limit of normal.

MAO-B Inhibitors

Drug	Confusion	Dizziness	Dyskinesia	Orthostatic complaints	Nausea
rasagiline (Azilect)[105]	>1	1 (1)	18 (10)	6-9 (3)	10-12 (8)
selegiline[106]	3-6	6-12	34 (19)	reported	10-20
selegiline (Zelapar)[107]	nr	11 (8)	6 (3)	<2	11 (9)

Adverse effects are reported as a percentage. Adverse effects are obtained from package inserts and are not meant to be comparative. Incidences for the placebo group are indicated in parentheses. nr = not reported.

Selegiline's MAO-B specific selectivity is not absolute even at the recommended daily dose of 10 mg. Rare cases of hypertensive reactions has been associated with the ingestion of tyramine-containing foods while on 10 mg dose.[108] The precise dose at which selegiline becomes non-selective is unknown but is estimated to be in the range of 30-40 mg/day.[109]

Rasagiline is approved without dietary restrictions except if high dose treatment is used resulting in the loss of selectivity above the recommended maximum dose. Rasagiline doses greater than 1 mg a day are not recommended due to the risk of hypertensive crisis and other adverse reactions.

Severe CNS toxicity (serotonin syndrome) has been reported with MAO-B inhibitors and antidepressant combinations. Rasagiline plasma concentration is increased when used in combination with ciprofloxacin or mild hepatic impairment. Patients with moderate or severe hepatic impairment should not use rasagiline.

Gabapentin Prodrug[110]

For both the 600 mg and 1,200 mg gabapentin enacarbil (Horizant) doses, somnolence/sedation and dizziness are the most common adverse effects. Balance disorder, edema, weight gain, blurred vision, disorientation, feeling drunk, lethargy and vertigo also occurred. In simulated driving studies, a daily single 1,200-mg dose gabapentin enacarbil caused significant driving impairment between 2 and 14 hours after dosing. The impairment was similar to that caused by the active control, a single oral dose of diphenhydramine 50 mg. The 600-mg dose was not studied. However since a 600 mg/day dose of gabapentin enacarbil can cause significant somnolence (similar to that of the 1,200 mg/day dose), the 600 and 1,200 mg/day doses may have similar effects on driving and a driving impairment warning was added to the package insert to warn patients not to dri8ve until they have gained sufficient experience with the drug and to assess their personal level of driving impairment. Augmentation and rebound, which have occurred with dopamine agonists, have not been reported with gabapentin enacarbil.[111]

SPECIAL POPULATIONS[112]

Pediatrics

Benztropine should not be used in children three years of age or younger. The safety and effectiveness have not been established in pediatric patients for any of the other agents reviewed for treatment of PD. The safety and efficacy of gabapentin enacarbil (Horizant), used in RLS, has not been established in pediatric patients.

Pregnancy

All agents in this class are Pregnancy Category C except for bromocriptine (Parlodel). Bromocriptine is Category B, but should not be used during lactation in postpartum women. Selegiline (generic, Zelapar) is Pregnancy Category C, but it also should not be used during lactation in postpartum women.

Hepatic Impairment

A study in patients with hepatic impairment has shown that moderate non-cirrhotic liver disease had no impact on the pharmacokinetics of tolcapone. However, a black box warning was added for patients with moderate cirrhotic liver disease (Child-Pugh Class B) because of the risk of potentially fatal, acute fulminant liver failure. The clearance and volume of distribution of unbound tolcapone was reduced by almost 50 percent thus increasing the unbound drug by twofold. If the patient exhibits clinical evidence of active liver disease or two SGPT/ ALT or SGOT/AST values greater than the upper limit of normal, tolcapone therapy should not be initiated. Patients who developed hepatocellular injury on past tolcapone therapy may have an increased risk of liver injury if tolcapone therapy is re-introduced. Analysis of the post marketing data indicates increases in SGPT/ALT or SGOT/AST, when present, generally occur within the first six months of treatment with tolcapone.[113]

Patients with mild hepatic impairment should have the dosage of rasagiline (Azilect) adjusted to 0.5 mg daily. Rasagiline should not be used in patients with moderate or severe hepatic impairment.

All of the other agents, except for benztropine and pramipexole should be used with caution in patients with hepatic impairment.

The influence of hepatic function impairment on pramipexole pharmacokinetics has not been evaluated. Because approximately 90 percent of the recovered dose is excreted in the urine as unchanged drug, hepatic function impairment would not be expected to have a significant effect on pramipexole elimination.

The pharmacokinetics of ropinirole have not been studied in patients with hepatic function impairment. Because patients with hepatic function impairment may have higher plasma levels and lower clearance, ropinirole should be titrated with caution in these patients.

Renal Impairment

Trihexyphenidyl and levodopa/carbidopa (Parcopa, Sinemet, Sinemet CR) should be used with caution in patients with renal impairment.

Pramipexole clearance correlates well with creatinine clearance; therefore, creatinine clearance can be used as a predictor of the extent of decrease in pramipexole clearance. Pramipexole dosage should be adjusted with renal impairment and creatinine clearance less than 60 mL/minute. In dialysis patients, pramipexole is minimally removed by dialysis and caution should be exercised for these individuals.

Ropinirole has not been studied in patients with severe renal impairment. Dosing adjustments are not needed in patients with moderate impairment.

All of the MAO-B inhibitors should be used with caution in patients with renal impairment.

The dosing frequency of gabapentin enacarbil (Horizant) should be altered in patients with renal impairment. For patients with an estimated creatinine clearance of 30-59 mL/min, 600 mg of gabapentin enacarbil should be administered on days one and three, then daily there after. Gabapentin enacarbil should not be used in patients with creatinine clearance <30 mL/min or in patients on hemodialysis.

Elderly

Pramipexole clearance decreases with age, as the half-life and clearance are about 40 percent longer and 30 percent lower, respectively, in elderly (65 years of age and older) compared with young, healthy volunteers (younger than 40 years of age). This difference is most likely due to the decrease in renal function with age, since pramipexole clearance is correlated with renal function.

Pharmacokinetic studies demonstrated a reduced clearance of ropinirole in elderly patients. Dosage adjustment is not necessary because the dose is individually titrated to clinical response.

DOSAGES[114,115,116,117,118,119,120,121,122,123,124,125, 126,127]

Parkinson's Disease

Therapeutic Class	Drug	Initial Dose	Maximum Daily Dose	Recommended Dosing Schedule	Availability
Anticholinergics	benztropine	0.5 mg	6 mg	one to two times daily	0.5, 1, 2 mg tablets
	trihexyphenidyl	1 mg	15 mg	three to four times daily	2, 5 mg tablets 2 mg/5 mL elixir
Dopamine precursor	carbidopa (Lodosyn)	25 mg	200 mg	three to four times daily	25 mg tablets
Dopamine precursor / dopa decarboxylase inhibitor	levodopa/carbidopa	25/100mg	200 mg carbidopa	three to four times daily	10/100, 25/100, 25/250 mg tablets
	levodopa/carbidopa ODT (Parcopa)	25/100mg	200 mg carbidopa	three to four times daily	10/100, 25/100, 25/250 mg disintegrating tablets
	levodopa/carbidopa controlled release	50mg/200mg	200 mg carbidopa	Twice daily	25/100, 50/200 mg sustained release tablets
MAO-B Inhibitors	rasagiline (Azilect)	0.5-1 mg	1 mg	once daily	0.5, 1 mg tablets
	selegiline (Eldepryl)	5 mg	10 mg	twice daily with breakfast and lunch	5 mg capsules; 5 mg tablets
	selegiline ODT (Zelapar)	1.25 mg	2.5 mg	once daily before breakfast and without liquid	1.25 mg disintegrating tablets
Dopamine agonists	bromocriptine (Parlodel)	1.25 mg	100 mg	twice daily with meals	2.5 mg Snap tablets; 5 mg capsules
	pramipexole (Mirapex)	0.125 mg	4.5 mg	three times daily	0.125, 0.25, 0.5, 0.75, 1, 1.5 mg tablets
	pramipexole ER (Mirapex ER)	0.375 mg	4.5 mg	once daily; swallow tablet whole and must not be chewed, crushed or divided	0.375, 0.75, 1.5, 2.25, 3, 3.75, 4.5 mg tablets
	ropinirole (Requip)	0.25 mg	24 mg	three times daily	0.25, 0.5, 1, 2, 3, 4, 5 mg tablets
	ropinirole ER (Requip XL)	2 mg	24 mg	once daily as a whole tablet and must not be chewed, crushed or divided	2, 4, 6, 8, 12 mg tablets
	rotigotine (Neupro)	Early stage: 2 mg Advanced stage: 4 mg	Early stage: 6 mg Advanced stage: 8 mg	once daily	1, 2, 3, 4, 6, 8 mg patch

Parkinson's Disease (continued)

Therapeutic Class	Drug	Initial Dose	Maximum Daily Dose	Recommended Dosing Schedule	Availability
COMT inhibitors	entacapone (Comtan)	200 mg	1,600 mg	200 mg with each dose of levodopa/carbidopa	200 mg tablets
	tolcapone (Tasmar)	100 mg	600 mg	three times daily	100, 200 mg tablets
Dopamine precursor/dopa decarboxylase inhibitor/COMT inhibitor	levodopa/carbidopa/ entacapone (Stalevo)	one tablet	Based on maximum dose of entacapone: 50,75,100, 125 and 150 mg: eight tablets/day:; Based maximum dose of carbidopa: 200 mg: six tablets/day:	every three to five hours	50/12.5/200, 75/18.75/200, 100/25/200, 125/31.25/200, 150/37.5/200, 200/50/200 mg tablets

Dosing conversion between the extended-release dopamine agonists (Requip XL, Mirapex ER) and their immediate-release counterparts can be found in the package insert of the extended-release products.[128,129]

Restless Leg Syndrome

Therapeutic Class	Drug	Initial Daily Dose	Maximum Daily Dose	Recommended Dosing Schedule	Availability
Dopamine agonists	pramipexole (Mirapex)	0.125 mg	0.75 mg	once daily two to three hours prior to bedtime	0.125, 0.25, 0.5, 0.75, 1, 1.5 mg tablets
	ropinirole (Requip)	0.25 mg	4 mg	once daily one to three hours prior to bedtime	0.25, 0.5, 1, 2, 3, 4, 5 mg tablets
	rotigotine (Neupro)	1 mg	3 mg	once daily	1, 2, 3, 4, 6, 8 mg patch
Gabapentin prodrug	gabapentin enacarbil (Horizant)	600 mg*	1,200 mg**	once daily	300, 600 mg tablets

*Gabapentin enacarbil is given as a single 600 mg dose once daily with food at approximately 5:00 PM.
**Clinical trials included a 1,200 mg dose; however, this dose resulted in increased adverse effects with no additional benefit.

CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this review. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for

analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

The clinical efficacy of antiparkinsons agents is determined in the literature primarily through the use of the total or partial Unified Parkinson Disease Rating Scale (UPDRS). Part I of the UPDRS is an evaluation of mentation, behavior, and mood. Part II is a self-reported evaluation of the Activities of Daily Living (ADL) and includes speech, swallowing, handwriting, ability to cut food, dressing, hygiene, falling, sialorrhea (salivation), turning in bed, and walking. Part III is a clinician-scored motor examination that is extensive and includes speech, resting tremor, facial expression and mobility, rigidity, hand and leg movements, gait, posture, and bradykinesia. Each item is rated on a scale of zero (normal) to four (can barely perform). Part IV is the Hoehn and Yahr staging scale and Part V is the Schwab and England ADL scale.[130]

Scales used to estimate health outcomes are the European Quality of Life Scale (EQ-5D) and Parkinson's disease quality of life scale (PDQUALIF). EQ-5D is a generic measure of health status, which provides a simplified descriptive profile and a single index value.[131] With this profile and index value, a clinical and economic evaluation of health care in population health surveys can be determined. PDQUALIF is a 33-item instrument evaluating seven domains: social/role function, self-image/sexuality, sleep, outlook, physical function, independence, and urinary function, plus one item of Global Health-Related Quality of Life (HRQOL).[132]

Parkinson's Disease

anticholinergics

There is a paucity of high-quality evidence supporting the use of anticholinergics in the treatment of PD. The benefits of these agents in the treatment of PD are well recognized throughout the medical community.

In one study of benztropine, 29 patients with mild to moderate PD and stabilized on levodopa/carbidopa were randomized in double-blind crossover fashion to receive benztropine or placebo.[133] Benztropine conferred significantly greater improvement than placebo as measured by the clinician and patient global assessment. Statistically significant improvements were noted in rigidity, finger tapping speed, and activities of daily living during the benztropine phase. There were no significant adverse events noted.

levodopa

Levodopa revolutionized the treatment of PD when it was introduced over 40 years ago. Although there is little evidence from high quality clinical trials to support its use, it is considered the gold standard for the treatment of PD.[134] The response to levodopa therapy in PD is seen as a dramatic

improvement in function and, often times, quality of life. Symptoms that usually respond to levodopa treatment include rigidity, tremor, bradykinesia, gait, and micrographia. Other symptoms of PD such as imbalance, dysarthria, sexual dysfunction, excessive sweating, sensory problems, and constipation do not always respond well to levodopa therapy.

levodopa/carbidopa IR (Sinemet) versus levodopa/carbidopa CR (Sinemet CR)

A total of 618 patients were studied in 36 centers worldwide in a blinded, randomized, parallel study.[135] Measures of efficacy and adverse effects were recorded at three-month intervals for five years. A patient diary and a physician-recorded questionnaire evaluated motor fluctuations and dyskinesias and the Nottingham Health Profile (NHP) evaluated quality of life. After five years, the mean dose of levodopa/carbidopa IR was 426 mg per day, and the bioavailable dose of levodopa/carbidopa CR was 510 mg per day (mean 736 mg per day). After five years, 20.6 percent of the levodopa/carbidopa IR group and 21.8 percent of the levodopa/carbidopa CR group had motor fluctuations or dyskinesia. Sixteen percent of both groups had changes in motor response by the questionnaire's definition. There was no significant difference between the two treatment groups.

levodopa/carbidopa (Sinemet) versus levodopa/carbidopa/entacapone (Stalevo)

The STRIDE-PD study evaluated 747 patients with PD over a period of 134 weeks.[136] In this double-blind trial, patients were randomized to levodopa/carbidopa or levodopa/carbidopa/ entacapone. The primary endpoint was time to onset of dyskinesia. The study found that patients taking levodopa/carbidopa/entacapone had a shorter time to onset and increased frequency of dyskinesia. While not significantly different, time to wearing off and motor scores did trend in favor of the levodopa/carbidopa/ entacapone group.

MAO-B Inhibitors

selegiline with levodopa/decarboxylase inhibitor (DDCI) versus levodopa/DDCI versus bromocriptine

Between 1985 and 1990, 782 patients were recruited into an open pragmatic multicenter trial and were randomized to receive levodopa/decarboxylase inhibitor (DDCI), levodopa/DDCI plus selegiline, or bromocriptine.[137] The patients were followed for ten years and results were reported from the Parkinson's Disease Research Group of the United Kingdom trial. The main endpoints evaluated were mortality, disability, and motor complications. Other endpoints assessed health-related quality of life and mental function. The median duration of follow-up at final assessment was 14 years in the 166 (21 percent) surviving participants, who could be contacted. After adjustment for baseline characteristics, disability scores were better in the levodopa than in the bromocriptine arm (Webster: 16.6 versus 19.8; p=0.03; Northwestern University Disability: 34.3 versus 30.0, p=0.05). Physical functioning (difference 20.8; 95% confidence interval (CI), 10.0-31.6; p<0.001) and physical summary scores (difference 5.2; 95% CI, 0.7-9.7; p=0.03) on the 36-item short-form health survey were also superior on levodopa. Differences in mortality rates and prevalence of dyskinesias, motor fluctuations, and dementia were not significantly different. Results demonstrate that there were no long-term advantages in terms of reducing mortality or motor disability to initiating treatment with bromocriptine compared with levodopa in early PD. Also, bromocriptine did not sustain the initial improvement in reduced frequency of motor complications. Selegiline combined with levodopa arm was prematurely terminated after six years due to increased mortality in patients. No evidence was demonstrated of a long-term benefit or clinically relevant disease-modifying effect with initial dopamine agonist treatment.

rasagiline (Azilect) versus entacapone (Comtan)

In an 18-week, double-blind, multicenter, randomized trial, the efficacy of rasagiline was compared to entacapone and placebo.[138] A total of 687 patients were randomly assigned to receive rasagiline (n=231; 1 mg once daily), entacapone (n=227; 200 mg with every levodopa dose), or placebo (n=229). The primary outcome measured was to determine the change in total daily off time, based on the intention-to-treat population. Other measures included the clinical global improvement (CGI) score and unified Parkinson's disease rating scale (UPDRS) scores, which was also based on the intention-to-treat population. Results demonstrated that both rasagiline and entacapone reduced mean daily off time (-1.18 hours for rasagiline and -1.2 hours for entacapone versus -0.4 hours for placebo; p=0.0001, p<0.0001, respectively), and increased daily on time without troublesome dyskinesia (0.85 hours versus 0.03 hours for placebo; p=0.0005 for both). Significant mean improvements in CGI scores were recorded (-0.86 for rasagiline and -0.72 for entacapone versus -0.37 for placebo; p<0.0001, p=0.0002, respectively). Changes in UPDRS scores also significantly improved for activities of daily living during off time (-1.71 for rasagiline and -1.38 for entacapone versus placebo; p<0.0001, p=0.0006, respectively) and motor function during on time (-2.94 and -2.73 versus placebo; both p<0.0001). Frequency of adverse events was similar for all treatments. Eighty-eight patients (13 percent) who were assigned treatment did not complete the study (n=23 rasagiline, n=30 entacapone, n=35 placebo), mainly due to withdrawal of consent (n=34) and adverse events (n=34). This study demonstrated that once-daily rasagiline reduces mean daily off time and improves symptoms of PD in levodopa-treated patients with motor fluctuations, but did not demonstrate superiority over entacapone.

In the Attenuation of Disease Progression with Azilect Given Once-Daily (ADAGIO) study, a placebo-controlled, double-blind, multicenter, randomized study in which 1,176 patients with untreated early parkinsons disease were randomly assigned to receive rasagiline 1 mg (n=288) or 2 mg (n=293) per day for 72 weeks or placebo (n=593) for 36 weeks followed by rasagiline 1 mg or 2 mg for 36 weeks.[139] Of 1,176 individuals, 266 (22.6 percent) did not complete the full study. The primary outcome measure was the need for additional antiparkinsonian therapy and changes in non-motor experience of daily living and fatigue scales, and changes in unified Parkinson's disease rating sale (UPDRS) scores between early versus delayed treatment. UPDRS scores were evaluated at 12, 26, 48, and 72 weeks. Results indicate rasagiline 1 mg had a smaller mean increase in UPDRS from weeks 12-36, less worsening of score from baseline to week 72 in the early start group and noninferiority between the delayed start group and the early-start group from weeks 48-72. Rasagiline 2 mg did not meet these end points. In nonmotor symptoms and rates of disease progression, rasagiline 1 mg and rasagiline 2 mg, reduced the need for additional antiparkinsonian therapy. At 36 weeks, when comparing the early start group versus the delayed-start group, the UPDRS motor subscores was improved with rasagiline 1 mg (mean difference -1.88; p<0.0001) and rasagiline 2 mg (mean difference -0.18; p<0.0001) relative to placebo At 72 weeks, the only improvement in UPDRS subscore between the early start group and the delayed-start groups was for the activities of daily living in the rasagiline 1 mg group. (-0.62; p=0.35). Rasagiline 1mg, a selective MAO-B inhibitor, delayed the need for symptomatic antiparkinson drugs and improved UPDRS scores to a greater extent for 72 weeks (p=0.2).

Dopamine Agonists

pramipexole (Mirapex) versus levodopa

A multicenter, parallel-group, double-blind, randomized, controlled trial compared initial treatment with pramipexole and levodopa in early Parkinson disease, followed by levodopa supplementation, with respect to the development of dopaminergic motor complications, other adverse events, and functional and quality-of-life outcomes.[140] The trial enrolled 301 patients with early Parkinson disease who required dopaminergic therapy to treat emerging disability. Subjects received 0.5 mg of pramipexole three times per day with levodopa placebo or 25/100 mg of carbidopa/levodopa three times per day with pramipexole placebo. The dosage was escalated during the first ten weeks for patients with ongoing disability. Thereafter, investigators were permitted to add open-label levodopa or other antiparkinsonian medications to treat ongoing or emerging disability. Patients initially on pramipexole had a significant reduction in the risk of developing dyskinesias (25 versus 54 percent; $p<0.001$) and wearing-off (47 versus 63 percent; $p=0.02$). Patients initially receiving levodopa had a significant risk reduction for freezing (25 versus 37 percent; $p=0.01$). At the end of two years, disabling dyskinesias and quality of life scores were similar in both groups. The mean improvement in the total Unified Parkinson's Disease Rating Scale (UPDRS) score from baseline to two years was greater in the levodopa group than in the pramipexole group ($p=0.003$). Compared with levodopa, pramipexole was associated with more somnolence (36 versus 21 percent, $p=0.005$) and edema (42 versus 15 percent, $p<0.001$). The study concluded that initial treatment with pramipexole resulted in lower incidences of dyskinesias and wearing off compared with initial treatment with levodopa. Initial treatment with levodopa resulted in lower incidences of freezing, somnolence, and edema and provided for better symptomatic control, as measured by the UPDRS, compared with initial treatment with pramipexole. Both options resulted in similar quality of life. Levodopa and pramipexole both appear to be reasonable options as initial dopaminergic therapy for Parkinson disease, but they are associated with different efficacy and adverse effect profiles.

The CALM-PD trial evaluated the development of motor complications in subjects with early PD randomized to initial treatment with either pramipexole or levodopa.[141] A secondary finding of the trial was a higher than anticipated development or worsening of somnolence and edema and development of hallucinations. In a secondary analysis of data from the CALM-PD trial, baseline patient characteristics were evaluated for their associations with the development or worsening of somnolence and edema and the development of hallucinations using Cox proportional hazards regression models. Kaplan-Meier estimates of the four-year incidence of the development or worsening of somnolence and edema and the development of hallucinations were 35 percent, 45 percent, and 17 percent of all patients, respectively. Somnolence was associated with initial pramipexole treatment, male gender, and greater than five systems with a comorbid illness. Edema was associated with initial pramipexole treatment, female gender, and comorbid cardiac disease. Hallucinations were associated with Mini-Mental State Examination score >28 and greater than five systems with comorbid illness. Comorbid illnesses are important and overlooked risk factors for the development of somnolence, edema and hallucinations. When initiating pramipexole therapy, patients must be monitored for somnolence and edema, and it should be realized that slight decrements in cognitive function and older age are associated with increased risk of hallucinations.

A two-year, open-label extension of the CALM-PD trial was added to the original four year trial.[142] Of the 301 patients that originally participated in the four-year study, 222 were enrolled in the open-label

two-year extension. The primary outcome was the time-weighted average of self-reported disability scores in the "on" and "off" states on the Schwab and England Activities of Daily Living (ADL) Scale at the final visit. The reported mean scores on this scale in the initial pramipexole and initial levodopa groups didn't differ at six years (79.9 versus 82.5, respectively; p=0.19). Initial treatment with levodopa more commonly led to adverse effects such as dopaminergic motor complications (68.4 percent for levodopa versus 50 percent for pramipexole; p=0.002), including wearing off, on-off effects, or dyskinesias, but disabling dyskinesias were uncommon in both groups. Scores on the Epworth Sleepiness Scale were significantly higher with initial pramipexole than initial levodopa (11.3 versus 8.6, respectively; p<0.001), indicating more sleepiness in the pramipexole group. Mean changes from baseline on the UPDRS were not statistically significant, but did favored levodopa (0.5 for levodopa versus 2.4 for pramipexole; p=0.11). This benefit was less than had been seen in the four-year trial.

A multicenter, parallel-group, double-blind, randomized, placebo-controlled trial evaluated the safety, tolerability, and efficacy of adjunctive pramipexole therapy in PD patients of African, Asian, or Hispanic heritage treated with levodopa.[143] One hundred forty-four PD patients of African, Asian, or Hispanic heritage enrolled from January 1997 to August 1998 and were observed until October 1998 at seventeen Parkinson Study Group sites in the United States and Puerto Rico. Subjects received pramipexole 0.375 mg per day to a maximum tolerated dose ≤4.5 mg per day over a six-week period or placebo, achieving optimum levels in the four-week maintenance period. The main outcome measure was the change in the sum of the UPDRS activities of daily living and motor skills from baseline to the tenth week. Parkinsonism improved with pramipexole, UPDRS score 10.27 at ten weeks, versus placebo, UPDRS score 6.54 at ten weeks (p=0.012) and was similar in each group. Adverse events occurred in 85 percent of patients on pramipexole and 69 percent on placebo. Hallucinations and insomnia were more common on pramipexole than placebo (p=0.023; p=0.045, respectively). Pramipexole is an effective adjunctive PD therapy in patients of African, Asian, or Hispanic heritage and tolerability and safety overall were similar among groups; however, differences in profiles of adverse effects and tolerability were suggested.

A randomized trial investigated the effect of therapy on HRQOL, and explored factors that influenced the HRQOL profiles and subdomains.[144] A total of 301 subjects with early Parkinson's disease were randomized to either initial pramipexole or initial levodopa, and then followed every three months over a four-year period. Health outcomes were estimated by using the EQ-5D and PDQUALIF, and the incremental effectiveness as the accumulated difference in the total HRQOL was calculated over time between treatments. The subgroup analyses (by sex, race, age, baseline patient characteristics, and occurrence of adverse events) were conducted using the same approach. Sensitivity analysis was performed to test the how missing data effected the results. The results indicated that all three HRQOL measures reported similar profiles over time characterized by initial improvement over the first three to six months, followed by a gradual decline in years two, three, and four. The difference in HRQOL between the treatment arms widened in favor of pramipexole in years three and four for all HRQOL measures used (EQ-5D: Year 3 0.048, p=0.03; Year 4 0.071, p=0.04). The analyses suggested that the effect of pramipexole on HRQOL was mediated through nonmotor functions; whereas, the effect of levodopa on HRQOL was mediated primarily through motor domains. These results indicate that pramipexole has an improved nonmotor effect and levodopa has an improved mobility effect, and these drugs affect the different domains to improve the patient's HRQOL differently.

ropinirole (Requip) versus levodopa

A five-year trial of ropinirole and levodopa in early PD showed that ropinirole is associated with reduced incidence of dyskinesias.[145] The post hoc analysis investigated whether the dyskinesia-sparing benefit of ropinirole is lost when levodopa is added to the regimen and evaluated other risk factors for developing dyskinesias. Patients receiving levodopa had a significantly higher risk of dyskinesias than those receiving ropinirole monotherapy (hazard ratio [HR], 6.67; 95% CI, 3.23 to 14.29; p<0.001). When patients randomized to ropinirole were treated with supplementary levodopa, the development of dyskinesias was not significantly different from that in those receiving levodopa from the start (HR, 0.80; 95% CI, 0.48 to 1.33; p=0.39). However, the onset of dyskinesias was delayed by approximately three years compared with levodopa monotherapy. The risk of developing dyskinesias during maintained initial ropinirole monotherapy is very low. Only once levodopa is added does the risk substantially change. Early use of ropinirole postpones the onset of dyskinesias, but these benefits decline when levodopa therapy is started, with no evidence of a subsequent rapid "catch-up" or a lasting preventive effect.

pramipexole (Mirapex) versus ropinirole (Requip)

Sixty patients with "de novo" idiopathic PD were randomized into one of two dopamine agonist monotherapy groups to receive oral ropinirole at 15 mg per day or pramipexole at 2.1 mg per day.[146] Dose of the dopamine agonist could be increased in the following two years but levodopa could not be added until the study, designed to investigate the possible occurrence of wearing-off during dopamine agonist monotherapy, ended. Wearing-off was assessed by self-evaluation charts confirmed by a blinded observation of a 30 percent or greater deterioration in the UPDRS motor score. Proc Mixed and Kaplan-Meier curves evaluated treatment variables as a function of time. T-tests were used to compare post hoc variables reclassified according to wearing-off occurrence. Thirty patients received ropinirole and 30 patients received pramipexole therapy. Eighteen patients (30 percent) experienced wearing-off 15 to 21 months after beginning monotherapy with no differences observed between the treatments. Statistical evaluation gave evidence of differences between patients who experienced wearing-off and those who did not; however, UPDRS scores deteriorated similarly. Study findings provide evidence of wearing-off phenomena in patients with early PD treated with non-ergot dopamine agonist monotherapy.

ropinirole immediate release (Requip) versus ropinirole ER (Requip XL)

Efficacy and Safety Evaluation in Parkinson's Disease (EASE-PD) monotherapy studied ropinirole ER and ropinirole immediate release.[147] The primary outcomes measured in the study were the relationship between ropinirole systemic exposure in terms of steady-state area under the curve between time zero and 24 hours after dose ($AUC_{(0\text{-}24,ss)}$), change from baseline in Unified Parkinson's Disease Rating Scale (UPDRS) total motor score, and awake time spent "off". In EASE-PD Monotherapy, the data demonstrated that the relationship between the decrease in UPDRS motor score and AUC(0-24,ss) was similar for both formulations, with a 60 percent to 80 percent probability of response for the exposure range studied. In patients with early PD, similar clinical benefit was achieved at AUC(0-24,ss) values associated with doses of 8 to 12 mg and higher doses (up to 24 mg). The results demonstrated that the exposure-response relationship was optimized with the dose range of 8 to 12 mg, providing the most clinical benefit for the improvement in UPDRS total motor score in patients with early PD. This study, however, did not demonstrate superiority of either the immediate release or extended release form of ropinirole.

pramipexole (Mirapex) versus pramipexole ER (Mirapex ER)

A randomized, double-blind, placebo-controlled, multicenter trial compared extended-release pramipexole, immediate-release pramipexole, and placebo in patients diagnosed with early PD.[148] Patients were initiated at 0.375 mg daily, followed by a flexible titration up to 4.5 mg daily, based on efficacy and tolerability. Patients on levodopa therapy at the outset of the trial were excluded, but levodopa was allowed as a rescue medication. Stable doses of MAO-B inhibitors, anticholinergics, or amantadine were allowed. The primary efficacy endpoint was the change from baseline in Parts II + III of the Unified Parkinson's Disease Rating Scale (UPDRS) after 18 weeks of treatment. Patients receiving extended-release pramipexole experienced a change of -8.1 points, versus -5.1 points with placebo ($p<0.03$).

rotigotine (Neupro) versus ropinirole (Requip), and placebo

A multicenter, double-blind, multinational, randomized, double-dummy, placebo- and ropinirole-controlled study in patients with early stages of PD with 561 patients randomized in a 2:2:1 ratio to receive either rotigotine, ropinirole, or placebo.[149] Under the double-dummy design, each patient took capsules (either placebo or active) and applied a patch (placebo or active) each day. Patients with ropinirole were titrated in a 13 week period to reach maximum dose of 24 mg/24 hours while patients with rotigotine used a 4 week titration schedule to reach a maximum dose of 8 mg/24 hours. Once a patient and investigator agreed about the optimal dose reached, the patient was then maintained on that dose throughout the 24 week maintenance period. The primary efficacy variable was the proportion of patients who responded to treatment. A "responder" was defined as a patient with a 20 percent or greater decrease in UPDRS Parts II + Parts III (motor) scores from the original baseline visit to the end of the double-blind maintenance period. A secondary efficacy variable includes absolute change in UPDRS II + III scores from the baseline visit to the end of the double-blind maintenance period, changes in UPDRS Part II and Part III subscale scores, and demonstration of noninferiority to ropinirole. Safety and tolerability was assessed by adverse events as reported by the patient or observed by the investigator. Dose to dose comparison was made from those receiving ropinirole **less than** 12 mg/day compared to rotigotine **less than** 8 mg/day. A total of 215 patients were assigned to rotigotine patch, 228 to oral ropinirole, and 118 to placebo. A total of 409 patients completed the study with 53 withdrawing from the ropinirole group, 62 withdrawing from the rotigotine group, and 33 withdrawing from the placebo group. The primary endpoint indicated treatment with rotigotine resulted in a higher proportion of responders (52 percent) compared with placebo (30 percent); $p<0.0001$. The ropinirole group proportion of responders (68 percent) when compared to placebo. In addition, other efficacy endpoints show significant improvement in absolute UPDRS Parts II + III subtotal score observed for patients in both the rotigotine and ropinirole mean decrease from baseline. For rotigotine, the mean decrease was -7.2 standard deviation ([SD]) $\pm$ 9.9) versus placebo -2.2 (SD $\pm$10.2) while ropinirole means decrease was -11 (SD+10.5) ($p<0.0001$). Common adverse events in the rotigotine group were application site reactions (17 percent), nausea (13 percent), dizziness (seven percent) and vomiting (six percent). Adverse events in the ropinirole group was nausea (16 percent), somnolence (12 percent), dizziness (eight percent), and vomiting (five percent). Placebo group adverse events include nausea (14 percent), somnolence (17 percent), and dizziness (nine percent). Serious adverse events (SAE) were reported in eight, ten, and 13% receiving placebo, rotigotine-treated and ropinirole-treated patients, respectively. Approximately five percent of patients receiving placebo, 17 percent of rotigotine treated patients, and 13 percent of ropinirole treated patients reported adverse events leading to discontinuation. As a result, the trial demonstrated that

transdermal rotigotine is safe and effective. The study reported 92 percent of rotigotine users were at the maximal doses whereas 26 percent of ropinirole users were at maximum dose.

rotigotine (Neupro) and placebo

A multicenter, double-blind, randomized study was performed with 277 patients with early-stage idiopathic PD for six months.[150] Patients were randomized to either rotigotine or placebo in a 2:1 ratio. Starting dose was 2 mg/24 h and titrated weekly to effective dose or 6 mg/24 h patch and maintained for six months. Primary efficacy measures were the change in the UPDRS scores (part II and III) from baseline to end of treatment and responder rates (patients with ≥20% improvement). The mean decrease in UPDRS subtotal scores was 3.98 (±0.707) points lower those receiving placebo ($p<0.0001$). UPDRS part III was -3.50 (±7.26) which contributed the most to the UPDRS improvement. The rotigotine group also had more responders than placebo group (48% versus 19%; $p<0.0001$). A total of 78 percent of the rotigotine group (n=142) completed the trial versus 84 percent of the placebo group (n=81). Adverse events were noted to be generally mild to moderate. The most commonly reported treatment emergent adverse event included application site reaction, nausea, somnolence, dizziness, and headache. The study observed significant differences between rotigotine group and placebo with relative well tolerance to the medication. At the conclusion of the study, study participants were offered the opportunity to enroll in a prospective, open-label study for up to six years at optimal dose (up to 16 mg/24h).[151] Adjunctive levodopa was allowed. Results from the six-year longitudinal study indicate the medication was well tolerated for up to six-years and that adverse effects reported were similar to those observed in shorter studies.

The PREFER study looked at advanced PD with its major treatment challenge to reduce "off" time. The "off" time is defined as a period in the day where the medication the patient is on no longer controls their symptoms. PREFER was a randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of two transdermal doses of rotigotine in subjects with advanced PD with ≥2.5 hours of daily "off" time.[152] Patients (n=351) were randomized to placebo patches (n=120), rotigotine 8 mg/24 h patches (n=120), or rotigotine 12 mg/24 h patches (n=111). The primary efficacy endpoint was the absolute number of daily hours in the "off" state. A secondary endpoint was the percentage of subjects achieving ≥3 0 percent response in absolute time spent "off" from baseline. In the rotigotine 8 mg/24 h group, the absolute change in daily "off" between baseline and the end of the maintenance phase averaged -2.7 hours (95% CI: -2.1, -3.4; $p<0.0001$). The 12 mg/24h group averaged -2.1 hours (95% CI:-1.5,-2.8; $p=0.0031$) versus the placebo group averaging -0.9 hours (95% CI -0.32, -1.51). Post hoc analysis concluded the difference in decrease between the 8 mg/24 h group and the 12 mg/24 hr group was not significant. The reviewers' note the secondary endpoints show that the 8 mg/24 hr and the 12mg/24 hr group had a higher proportion of subjects with a ≥ 30 percent decrease in absolute "off" time at 56.6 percent and 55.1 percent, respectively.

The RECOVER study is a double-blind, placebo controlled trial, where 287 subjects with unsatisfactorily early morning motor symptom control were randomized in a 2:1 ratio to receive rotigotine or placebo.[153] Efficacy end points was improvement from baseline to end of maintenance in UPDRS Part III as -3.55 (95% CI, -5.37, -1.73; p-0.00002 and -4.26 (95% CI, -6.08, -2.45; $p<0.0001$). The reviewers' note the study results show clinically significant improvement with the use of rotigotine for early morning motor impairment and nocturnal sleep disturbance.

rotigotine versus pramipexole

In another double-blind, double-dummy randomized study to evaluate the wearing off type motor fluctuations seen in advanced PD, a controlled trial study (CLEOPATRA-PD) with 506 patients was randomized into rotigotine (up to 16 mg/24h), pramipexole (4.5 mg/day), or placebo for 6 months.[154] Mean absolute change in off time from baseline compared with placebo was -1.58 hours (95% CI, -2.27 to -0.90; p<0.0001) for rotigotine and -1.94 hours (-2.63 to -1.25; p<0.0001) for pramipexole. The reviewers' note these results show rotigotine and pramipexole were equally efficacious for change in absolute off time from baseline. Responder rates for pramipexole were slightly improved over rotigotine at 67 percent versus 59.7 percent while placebo was at 35 percent. Both drugs were well tolerated and had similar adverse effect profiles.

COMT Inhibitors

entacapone (Comtan) versus tolcapone (Tasmar)

A multicenter, double-blind, randomized, active-control trial involving 150 patients with advanced, fluctuating PD examined the efficacy and safety of replacing entacapone with tolcapone.[155] Patients receiving entacapone at least 15 or more days were randomly assigned to continue entacapone (n=75) or switch to tolcapone (n=75) and were followed for three weeks. Efficacy measures included changes in on time (without disabling dyskinesia) and an investigator's global assessment (IGA). The on time increased by greater than or equal to one hour per day (primary efficacy measure) in 43 percent of entacapone-treated patients and 53 percent of tolcapone-treated patients, and by greater than or equal to three hours per day in 13 percent and 25 percent, respectively. The IGA indicated moderate to marked improvements in 25 percent of entacapone patients and 39 percent receiving tolcapone. Response rates (the proportion of patients with greater than or equal to 1 hour per day increase in on time and improvements on IGA) were 17 percent with entacapone and 32 percent with tolcapone. Dyskinesia was the most common adverse event affecting 29 percent of entacapone and 31 percent of tolcapone recipients. One patient in each group had elevated liver enzymes, resulting in treatment withdrawal (levels returned to normal thereafter in both cases). Tolcapone did offer increased on time in more patients than the entacapone and also demonstrated moderate to marked improvements in more patients than the entacapone per the IGA. Statistical analysis was not reported to substantiate the statistical significance of the data, but tolcapone was clinically more efficacious in this patient population.

entacapone (Comtan) versus rasagiline (Azilect)

In the LARGO (Lasting effect in Adjunct therapy with Rasagiline Given Once daily) trial, 687 patients were randomized in double-blind fashion to receive entacapone, rasagiline, or placebo for 18 weeks.[156] Between 85 and 90 percent of patients in each group completed the study. Total daily off time decreased by 21 percent (1.2 hours) with both active treatments compared to seven percent (0.4 hours) with placebo (p<0.0001 for both comparisons to placebo). This was associated with a 0.9-hour increase in on time in the active treatment groups compared to a 0.03-hour increase with placebo (p=0.0005). Compared to placebo, entacapone and rasagiline significantly improved UPDRS ADL off time (p=0.0006 and p<0.0001, respectively), UPDRS motor function during on time (p<0.0001 for both agents), and CGI scores (p=0.0002 and p<0.0001, respectively). There was no between-group difference in the incidence of dyskinesia (approximately five percent in each group).

Restless Leg Syndrome (RLS)

levodopa versus placebo

Seven randomized, double-blind, placebo-controlled trials consistently demonstrate the efficacy of levodopa in the treatment of RLS.[157,158,159,160,161,162,163] Although these trials included a relatively small number of patients (six to 41 patients per trial), the data have resulted in the American Academy of Sleep Medicine designating levodopa as a standard for the treatment of RLS.[164]

pramipexole (Mirapex) versus placebo

In a double-blind study, 339 patients (ages 18 to 80 years) with RLS were randomized to receive placebo or pramipexole 0.25, 0.50 or 0.75 mg daily for 12 weeks.[165] At the end of the study, the mean score on the International Restless Legs Scale (IRLS) change from baseline, the primary endpoint, was greater in patients receiving each dose of pramipexole than in those receiving placebo (all doses $p<0.01$); there was no significant difference between the three pramipexole dosages. Response, defined as a CGI-I score that was "much improved" or "very much improved", occurred in 72 percent of patients receiving pramipexole and 51.2 percent of patients receiving placebo.

A six-week, randomized, placebo-controlled study evaluated the efficacy of pramipexole versus placebo in RLS.[166] Initially 345 patients were randomly assigned in a 1:2 ratio to receive either placebo (n=115) or pramipexole (n=230). The patient demographics and baseline characteristics were comparable between treatment groups. Initial dose of pramipexole was 0.125mg per day and was optimized using the Patient Global Impression (PGI) assessment to a maximum of 0.75 mg per day if necessary. The primary endpoints evaluated at week six were the change from baseline in the International RLS Study Group Rating Scale (IRLS) and the proportion of patients reporting "much to very much improved" results with Clinical Global Impressions-Improvement (CGI-I) assessments. Secondary endpoints assessed PGI and IRLS responder rates. At baseline, mean IRLS scores were 24.9 for placebo and 24.7 for pramipexole, indicating severely affected patients. After six weeks, adjusted mean reductions in IRLS score were 5.7± 0.9 for placebo (median dose 0.47 mg/day) and 12.3±0.6 for pramipexole (median dose 0.35 mg/day)($p<0.0001$). CGI-I responder rates were 32.5 percent for placebo and 62.9 percent for pramipexole ($p<0.0001$). For all secondary endpoints, pramipexole showed superior results. Pramipexole was well tolerated throughout the study.

A 12-week, randomized, placebo-controlled study evaluated the ability of pramipexole to improve sleep and decrease RLS symptoms.[167] Adults with moderate or severe RLS were randomized to receive placebo or pramipexole, which was flexibly titrated from 0.25 to 0.75 mg, two to three hours before bedtime. The primary outcome measures were changes in Medical Outcomes Study (MOS) sleep disturbance score and International RLS Study Group Rating Scale (IRLS) score at 12 weeks. The intent-to-treat population included 357 patients, 178 patients received pramipexole and 179 patients received placebo. At 12 weeks, the adjusted mean change from baseline was greater for pramipexole versus placebo for IRLS score (-13.4±0.7 versus -9.6±0.7, respectively) and MOS sleep disturbance score (-25.3±1.5 versus -16.8±1.5, respectively) ($p\leq0.0001$). Responder rates for CGI, PGI, and IRLS were also higher in the pramipexole group. RLS-QOL score was improved over placebo at week 12 ($p<0.01$) as were MOS sleep adequacy ($p=0.0008$) and quantity ($p=0.08$) scores. Nine percent of patients in each group withdrew because of adverse events.

A three-week, randomized, double-blind, placebo controlled, dose-finding study was performed in patients with moderate to severe RLS.[168] Patients (n=109) were randomized to receive between 0.125

to 0.75 mg per day of pramipexole or placebo. Polysomnographic (PSG) measures were taken along with patient and clinician ratings to evaluate the effectiveness of various doses on RLS. Results demonstrated that the periodic limb movements during time in bed index (PLMI) decreased significantly in each pramipexole dose group (adjusted mean difference in log-transformed data: 0.125 mg, -1.54; 0.25 mg, -1.93; 0.5 mg, -1.89; and 0.75 mg, -1.52; p<0.0001). Also, the International RLS Study Group Rating Scale (IRLS) scores were significantly reduced in all doses, with the greatest adjusted mean reduction in the 0.5 mg group (-17.01). All doses, except the lowest pramipexole dose demonstrated a higher percentage of responders (≥50 percent reduction of IRLS score) than for placebo (61.9-77.3, versus 33.3 percent). In the pramipexole groups, 50 percent to 77.3 percent of patients rated their condition as 'much better' or 'very much better', compared with 38.1 percent of patients in the placebo group (p=0.0139 for the 0.5 mg dose). Clinical global impressions (CGI) scale ratings of 'much improved' or 'very much improved' were given to 61.9 percent to 86.4 percent of patients in the pramipexole groups, compared with 42.9 percent in the placebo group (p<0.05 for the 0.25 mg, 0.5 mg, and 0.75 mg groups). Pramipexole was well tolerated and did not produce somnolence at any dose.

ropinirole (Requip) versus placebo

In a 12-week, double-blind, placebo-controlled, flexible-dose study, 381 patients were randomized to ropinirole (0.25-4.0 mg as needed and tolerated, once daily, 1 to 3 hours before bedtime) or placebo.[169] Significant treatment differences favoring ropinirole, compared with placebo, were observed for change in IRLS total score at week 12 (p<0.001), the primary endpoint, as well as for improvement in CGI-I at weeks one and 12. Ropinirole was associated with significantly greater improvements in subjective measures of sleep disturbance, quantity, and adequacy, as well as quality of life and anxiety. Although treatment differences favoring ropinirole in daytime somnolence were observed, they were not statistically significant (p=0.10). Ropinirole was generally well tolerated, with an adverse event profile consistent with other dopamine agonists.

In a double-blinded, placebo-controlled, parallel-group study, 65 patients with RLS and periodic leg movements in sleep (PLMS) were randomized to ropinirole (0.25-4.0 mg per day) or placebo for 12 weeks.[170] In the study, PLMS per hour decreased more with ropinirole (48.5 to 11.8), compared with placebo (35.7 to 34.2) (p<0.0001). Periodic limb movements with arousal per hour decreased from 7.0 to 2.5 with ropinirole but increased from 4.2 to 6.0 with placebo (p=0.0096). Periodic limb movements while awake per hour decreased from 56.5 to 23.6 with ropinirole but increased from 46.6 to 56.1 with placebo (p<0.0001). Ropinirole treatment significantly improved patients' ability to initiate sleep (p<0.05) and the amount of Stage 2 sleep (p<0.001) compared with placebo. There were no significant differences between groups in total sleep time and sleep efficiency. Sleep adequacy, measured subjectively, was significantly improved with ropinirole treatment (p=0.032). In contrast, the placebo group showed a greater increase in Stage 3/4 sleep (p<0.01). No serious adverse events occurred in either group. The study concluded that ropinirole is effective in the treatment of both the sleep and waking symptoms of RLS.

A 36-week study investigated the long-term efficacy of ropinirole in patients with RLS and evaluated the potential for relapse after discontinuation of active treatment.[171] Patients with primary RLS (n=202) received single-blind ropinirole for 24 weeks, and after meeting treatment continuation criteria were randomized for an additional 12 weeks to double-blind treatment with ropinirole or placebo. The primary efficacy measure was the proportion of patients relapsing during double-blind

treatment. Additional efficacy measures included time to relapse, withdrawals due to lack of efficacy, improvement on the CGI-I scale, change in IRLS score during double-blind treatment, and changes in sleep and QOL parameters. Significantly fewer patients relapsed on ropinirole (32.6 percent) versus placebo (57.8 percent) (p=0.0156). Time to relapse was longer with ropinirole, and more patients on placebo withdrew from the study due to lack of efficacy. Patients showed improvements in IRLS and CGI-I scores, sleep and QOL parameters with single-blind ropinirole. These efficacy measures were better maintained during the double-blind phase with ropinirole, but reduced with placebo. Ropinirole was well tolerated, and adverse events were typical for dopamine agonists.

In a double-blind, randomized, 12-week study, 267 patients with moderate to severe RLS were randomly assigned to ropinirole (0.25-4.0 mg/day) or placebo, one to three hours before bedtime.[172] Improvements were significantly greater for ropinirole than placebo for the primary endpoint; the change in IRLS score at week 12 (p=0.02). Ropinirole was also superior to placebo in showing improvement of CGI-I, as well as sleep and quality of life parameters.

rotigotine versus placebo

In a randomized, double-blind, placebo-controlled weekly dose efficacy trial, 458 patients with moderate to severe idiopathic RLS were randomly assigned to transdermal rotigotine 1 mg/24 h, rotigotine 2 mg/24 h, rotigotine 3 mg/24 h or placebo for six months.[173] Primary outcomes were absolute change from baseline to end of maintenance in IRLS sum score and the clinical global impressions (CGI) item 1 score which is defined as a 50 percent improvement in the respective score at the end of the maintenance versus baseline. A total of 68 percent of patients completed the study. The IRLS sum score and the CGI score improved during the titration phase and remained stable during the maintenance phase. All three strengths indicate treatment differences against placebo for RLS when measured with IRLS or CGI item 1 score (1mg/24 h, -5.1; 2 mg/24 h, -7.7; 3 mg/24 h, -8.2 (95% CI: p<0.0001). Rotigotine efficacy increases with increasing dose from 1 mg to 3 mg.[174] The long-term efficacy of rotigotine up to 4 mg/24 h in the treatment of RLS (n=295) was assessed in a five-year study (OLE trial). The study found that efficacy was maintained for up to five years at a level consistent with the initial 6-week double-blind trial.[175]

A randomized, double-blinded, placebo-controlled trial assessed efficacy and safety of rotigotine in the treatment of idiopathic RLS over a 6-month maintenance period.[176] Patients (n=505) were randomly assigned to five groups to receive either placebo or rotigotine (0.5, 1, 2, or 3 mg/24 hr) delivered by once-daily transdermal patch. The two co-primary efficacy parameters decreased from baseline to end of maintenance in IRLS sum score and in clinical global impressions (CGI-1) score. On both primary measures, 2 and 3 mg/24 hr rotigotine was superior to placebo (p<0.001). Adjusted treatment differences to placebo for the IRLS sum score were -4.5 (95% CI: -6.9, -2.2) for 2 mg/24 hr rotigotine, -5.2 (95% CI: -7.5, -2.9) for 3 mg/24 hr rotigotine, and for CGI item 1 -0.65 (95% CI: -1.0, -0.3) and -0.9 (95% CI: -1.3, -0.5) for the 2 and 3 mg/24 hr doses, respectively. Skin reactions (27%) and dopaminergic side effects such as nausea (18.1 percent) and headache (11.6 percent) were mostly mild or moderate in rotigotine. Rotigotine transdermal patches releasing 2 to 3 mg/24 hr significantly reduced the severity of RLS symptoms. Treatment efficacy was maintained throughout the 6-month double-blind period.

gabapentin enacarbil versus placebo

A 12-week double-blind, placebo-controlled study randomized subjects (n=325) (1:1:1) to gabapentin enacarbil 1,200 mg (n=113), gabapentin enacarbil 600 mg (n=115), or placebo (n=97).[177] The mean change from baseline in International Restless Legs Scale (IRLS) total score and proportion of responders rated "very much" or "much" improved on the Clinical Global Impression-Improvement Scale (CGI-I) at week 12 were the co-primary endpoints. A total of 42 patients withdrew from the study prior to completion with 79 percent in placebo (n=77); 87 percent in gabapentin enacarbil 1,200 mg (n=98); and 90 percent in gabapentin enacarbil 600 mg (n= 104) completing the study. Gabapentin enacarbil 1,200 mg mean had a IRLS total score at week 12 compared with placebo with the adjusted mean treatment difference for change from baseline of -3.5 [95% CI:-5.6, -1.3;p=0.0015). Gabapentin enacarbil 600 mg group had a mean IRLS total score at week 12 compared to placebo with the adjusted mean treatment difference for change from baseline of -4.3 (95% CI=6.4, -2.3; p<0.0001). On the CGI-I ratings where responders rated "much" or "very much" at week 12, the adjusted odds ratio for gabapentin enacarbil 1,200 mg is 4.3 (95% CI: 2.34, 7.86; p<0.0001) and gabapentin enacarbil 600 mg 3.3 (95% CI: 1.84, 5.99; p<0.0001. The most commonly reported treatment-emergent adverse events overall with gabapentin enacarbil 1,200 mg and 600 mg were dizziness and somnolence. Statistically significant differences (p<0.05) were also observed in another 12-week randomized, double-blind, placebo-controlled study (n=220) between gabapentin enacarbil 1,200 mg and placebo at 12 weeks for both the mean change from baseline in the IRLS Scale total score and the proportion of responders ("much improved" or "very much improved") on the CGI-I Scale.[178,179]

SUMMARY

Parkinson's Disease

Although dopamine agonists are effective adjuncts to levodopa in patients who begin to experience motor complications with levodopa, evidence suggests preferably using these agents as initial symptomatic therapy to reduce the risk for development of these motor complications. When used in early PD, dopamine agonists indicated for monotherapy, such as pramipexole (Mirapex, Mirapex ER), ropinirole (Requip, Requip XL), and rotigotine (Neupro), delay the need for levodopa treatment and its adverse effects. In general, monotherapy with these dopamine agonists is effective in a majority of patients for one year or less. A minority of patients may obtain benefits for periods as long as three years or more. In advanced disease, dopamine agonists increase "On" time and allow decreases in levodopa dose. Pramipexole, and rotigotine may reduce the risk of development of dyskinesias compared to levodopa. Ropinirole ER, ropinirole, and rotigotine demonstrated similar efficacy and safety in UPDRS motor scores in clinical trials. All the dopamine agonists reported mild to moderate adverse effects.

Dopamine agonists do not treat all features of PD, such as freezing, postural instability, autonomic dysfunction, and dementia, nor have they been shown to stop disease progression. Dopamine agonists are associated with neuropsychiatric, sedative, and other agonist-specific side effects, such as hallucination, symptomatic hypotension and psychosis. The non-ergot dopamine agonists, pramipexole, ropinirole, and rotigotine, might be better tolerated and cause fewer serious side effects than the older ergot agents such as bromocriptine (Parlodel). The risk of hypotension and somnolence appears to be higher with ropinirole than with pramipexole, while pramipexole appears to have a higher risk of hallucinations than ropinirole. Pramipexole and ropinirole carry bolded type warnings as patients report

falling asleep while engaged in the activities of daily living, although all anti-parkinson's agents now carry a class warning regarding the risk of "sleep attacks". Rotigotine is a dopamine agonist in a topical patch formulation which provides drug in a continuous delivery.

Levodopa/carbidopa (Parcopa, Sinemet, Sinemet CR), with or without a COMT inhibitor, should be added when dopamine agonist monotherapy no longer provides adequate control of the patient's symptoms. Treatment with levodopa/carbidopa benefits virtually all patients with PD. Although effective for the treatment of PD, levodopa/carbidopa is associated with motor fluctuations (wearing off, on-off phenomenon, dose failures, freezing episodes) and dyskinesia (peak-dose, diphasic, dystonic), especially problematic in patients with young-onset PD. Levodopa in combination with carbidopa is available in both immediate-release and controlled-release formulations. Levodopa/carbidopa should be titrated up slowly to avoid side effects such as nausea, vomiting, and hypotension.

Selegiline (generic, Zelapar) has been used historically as a neuroprotective agent. After a review of the literature, the American Academy of Neurology reported that selegiline has a mild symptomatic benefit, but clinical evidence for neuroprotective benefit is nonexistent. Because orally disintegrating selegiline tablets avoid the first pass effect, clinical effectiveness can be achieved at lower doses than with conventional selegiline tablets, and results in lower concentrations of amphetamine metabolites. When used as an adjunct to levodopa, rasagiline (Azilect) and selegiline do reduce motor fluctuations and increase "On" time; they also have levodopa-sparing effect. Rasagiline has an indication for monotherapy of PD. Based on the evidence, rasagiline would appear to be most effective in early PD. Unlike selegiline, rasagiline is an aminoindan derivative with no amphetamine metabolites.

The COMT inhibitors, tolcapone (Tasmar) and entacapone (Comtan), as adjunctive therapy to levodopa provide another therapeutic option for patients with advanced PD. These agents are easy to administer and require no dosage titration. The COMT inhibitors prolong the half-life and duration of action of levodopa and allow for a reduction in levodopa dose. They provide relief from the end-of-dose wearing-off phenomenon seen with levodopa. COMT inhibitors may reduce the risk for motor complications if used from the onset of levodopa therapy and have been shown to improve motor and ADL scores in stable levodopa responders. Side effects of COMT inhibitors include dyskinesia (due to increased dopamine), nausea, vomiting, diarrhea, hypotension, and neuropsychiatric problems. Tolcapone use is limited by its potential to cause liver injury.

Anticholinergics have some antiparkinsonian efficacy, particularly with respect to tremor, but they are relatively ineffective for the more disabling features of PD. They are also associated with muscarinic and cognitive side effects and may be associated with withdrawal effects.

Restless Leg Syndrome

Pharmacologic treatments have been used to alleviate symptom severity and improve quality of life and, historically, RLS has been treated with opioids, benzodiazepines, anticonvulsants, iron replacement, and dopaminergic agents but newer studies suggest that RLS is associated with the dopamine system and depletion of iron stores.

The American Journal of Medicine RLS guidelines report that dopamine agonist therapies appear to be effective and relieve symptoms rapidly. Rotigotine (Neupro) is a dopamine agonist formulated in patch form as once-daily dosing. The 2012 American Academy of Sleep Medicine RLS practice guidelines recommend pramipexole (Mirapex), ropinirole (Requip) and the extended-release gabapentin prodrug,

gabapentin enacarbil (Horizant) for RLS. Gabapentin enacarbil is associated with significant sedation/dizziness.

REFERENCES

1 Benztropine (Cogentin). Available at www.clinicalpharmacology.com. Accessed July 24, 2014.
2 Trihexyphenidyl (Artane). Available at www.clinicalpharmacology.com. Accessed July 24, 2014.
3 Carbidopa (Lodosyn). Available at www.clinicalpharmacology.com. Accessed July 24, 2014.
4 Sinemet [package insert]. Princeton, NJ; BMS; July, 2014.
5 Carbidopa-levodopa ODT (Parcopa). Available at www.clinicalpharmacology.com. Accessed July 30, 2014.
6 Azilect [package insert]. Kansas City, MO; Teva; June, 2014.
7 Selegiline (Eldepryl). Available at www.clinicalpharmacology.com. Accessed July 30, 2014.
8 Zelapar [package insert]. Costa Mesa, CA; Valeant Pharmaceuticals; February 2008.
9 Parlodel [package insert]. Suffern, NY; Novartis; January 2012.
10 Mirapex [package insert]. Ridgefield, CT; Boehringer Ingelheim; March 2013.
11 Mirapex ER [package insert]. Ridgefield, CT; Boehringer Ingelheim; May, 2014.
12 Requip [package insert]. Research Triangle Park, NC; GlaxoSmithKline; April 2009.
13 Requip XL [package insert]. Research Triangle Park, NC; GlaxoSmithKline; December 2012.
14 Neupro [package insert]. Smyrna, GA; UCB, Inc; April 2012.
15 Comtan [package insert]. East Hanover, NJ; Novartis; June 2014.
16 Tasmar [package insert]. Costa Mesa, CA; Valeant Pharmaceuticals; May 2013.
17 Stalevo [package insert]. East Hanover, NJ; Novartis; July 2014.
18 Horizant [package insert]. Research Triangle Park, NC; GlaxoSmithKline; July 2013.
19 Paha R, Factor SA, Lyons KE, et al. Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review). Neurology. 2006; 66:983-95.
20 Beers MH, Berkos R, eds. The Merck Manual of Geriatrics. 3rd ed. Whitehouse Station, NJ: Merck & Co; 2000:432-41.
21 Parkinson's Disease Handbook: A guide for patients and their families. American Parkinson Disease Association, Inc. 2005.
22 Beers MH, Berkos R, eds. The Merck Manual of Geriatrics. 3rd ed. Whitehouse Station, NJ: Merck & Co; 2000:432-41.
23 Beers MH, Berkos R, eds. The Merck Manual of Geriatrics. 3rd ed. Whitehouse Station, NJ: Merck & Co; 2000:432-41.
24 Marsden CD. Problems with long-term levodopa therapy for Parkinson's disease. Clin Neuropharmacol. 1994; 17:S32-44.
25 Chen JJ. Management of wearing off in Parkinson's disease. Consult Pharm. 2005; supp B:S15-21.
26 Beers MH, Berkos R, eds. The Merck Manual of Geriatrics. 3rd ed. Whitehouse Station, NJ: Merck & Co; 2000:432-41.
27 Beers MH, Berkos R, eds. The Merck Manual of Geriatrics. 3rd ed. Whitehouse Station, NJ: Merck & Co; 2000:432-41.
28 Isaacson SH. Parkinson's disease: an overview of current treatment options. Consult Pharm. 2005; supp B:S6-14.
29 Beers MH, Berkos R, eds. The Merck Manual of Geriatrics. 3rd ed. Whitehouse Station, NJ: Merck & Co; 2000: 432-41.
30 Hughes AJ, Ben-Shlomoa Y, Daniel SE, et al. What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinical pathologic study. Neurology. 1992; 42:1142-46.
31 Marsden CD, Parkes JD. "On-off" effects in patients with Parkinson's disease on chronic levodopa therapy. Lancet. 1976; 1:292-6.
32 Obeso JA, Rodriguez-Oroz MNC, Chana P, et al. The evolution and origin of motor complications in Parkinson's disease. Neurology. 2000; 55(Suppl 4):S13-20.
33 Lang AE, Lozana AM. Parkinson's disease. N Engl J Med. 1998; 339:1044-53.
34 Available at www.parkinson.org/Parkinson-s-Disease/Treatment/Medications-for-Motor-Symptoms-of-PD/MAO-B-inhibitors. Accessed August 8, 2014.
35 Koller WC, Silver DE, Lieberman A. An algorithm for the management of Parkinson's disease. Neurology. 1994; 44(12 suppl 10):S1-52.
36 Isaacson SH. Parkinson's disease: an overview of current treatment options. Consult Pharm. 2005; supp B:S6-14.
37 Rascol O, Brooks DJ, Korczyn AD, et al. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. N Engl J Med. 2000; 342:1484-91.
38 Isaacson SH. Parkinson's disease: an overview of current treatment options. Consult Pharm. 2005; supp B:S6-14.
39 Pahwa R, Factor SA, Lyons KE, et al. Practice Parameter: Treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review). Neurology. 2006; 66:983-95.
40 CG Goetz, W Poewe, O Rascol, et al. Evidence-based medical review update: Pharmacological and surgical treatments of Parkinson's disease: 2001 to 2004. Movement Disorders. 2005; 20:523-39.
41 Aurora RN, Kristo DA, Bista SR. The treatment of restless legs syndrome and periodic limb movement disorder in adults—an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses. An American Academy of Sleep Medicine Clinical Practice Guideline. Sleep. 2012; 35(8):1039-1062. Available at: http://www.aasmnet.org/Resources/PracticeParameters/TreatmentRLS.pdf. Accessed August 8, 2014.
42 Hening W. Current Guidelines and Standards of Practice for Restless Legs Syndrome. The American Journal of Medicine. 2007;120:S22-S27.
43 Hening W. Current Guidelines and Standards of Practice for Restless Legs Syndrome. The American Journal of Medicine. 2007;120:S22-S27.
44 Silber MH, Ehrenberg BL, Allen RP, et al. An algorithm for the management of restless legs syndrome. Mayo Clin Proc. 2004; 79(7):916-922.
45 Aurora RN, Kristo DA, Bista SR. The treatment of restless legs syndrome and periodic limb movement disorder in adults—an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses. An American Academy of Sleep Medicine Clinical Practice Guideline. Sleep. 2012; 35(8):1039-1062. Available at: http://www.aasmnet.org/Resources/PracticeParameters/TreatmentRLS.pdf. Accessed August 8, 2014.
46 Garcia-Borreguero D, Larrosa O, de la Llave Y, et al. Treatment of restless legs syndrome with gabapentin: a double-blind, cross over study. Neurology. 2002; 59:1573-9.
47 Happs S, Klosch G, Saletu B, et al. Treatment of idiopathic restless legs syndrome (RLS) with gabapentin. Neurology. 2001; 57:1717-9.
48 Gidal BE, Radulovic LL, Kruger S, et al. Inter- and intra-subject variability in gabapentin absorption and absolute bioavailability Epilepsy Res. 2002; 40:123-7.
49 Available at: www.clinicalpharmacology.com. Accessed July 30, 2014.

50 Available at: www.clinicalpharmacology.com. Accessed July 30, 2014
51 Benztropine (Cogentin). Available at: www.clinicalpharmacology.com. Accessed July 30, 2014
52 Trihexyphenidyl (Artane). Available at: www.clinicalpharmacology.com. Accessed July 30, 2014.
53 Sinemet [package insert]. Princeton, NJ; BMS; July, 2014.
54 Carbidopa-levodopa ODT (Parcopa). Available at at www.clinicalpharmacology.com. Accessed July 30, 2014.
55 Azilect [package insert]. Kansas City, MO; Teva; June 2014.
56 Selegiline (Eldepryl). Available at: www.clinicalpharmacology.com. Accessed July 30, 2014.
57 Zelapar [package insert]. Costa Mesa, CA; Valeant Pharmaceuticals; February 2008.
58 Parlodel [package insert]. Suffern, NY; Novartis; January 2012.
59 Mirapex [package insert]. Ridgefield, CT; Boehringer Ingelheim; March 2013.
60 Mirapex ER [package insert]. Ridgefield, CT; Boehringer Ingelheim; May 2014.
61 Requip [package insert]. Research Triangle Park, NC; GlaxoSmithKline; April 2009.
62 Requip XL [package insert]. Research Triangle Park, NC; GlaxoSmithKline; December 2012.
63 Neupro [package insert]. Smyrna, GA; UCB, Inc; April 2012.
64 Comtan [package insert]. East Hanover, NJ; Novartis; June 2014.
65 Tasmar [package insert]. Costa Mesa, CA; Valeant Pharmaceuticals; May 2013.
66 Horizant [package insert]. Research Triangle Park, NC; GlaxoSmithKline; July 2013.
67 Stalevo [package insert]. East Hanover, NJ; Novartis; July 2014.
68 Tasmar [package insert]. Costa Mesa, CA; Valeant Pharmaceuticals; May 2013.
69 Carbidopa; levodopa. Available at: www.clinicalpharmacology.com. Accessed July 30, 2014.
70 Benztropine (Cogentin). Available at: www.clinicalpharmacology.com. Accessed July 30, 2014.
71 Trihexyphenidyl (Artane). Available at: www.clinicalpharmacology.com. Accessed July 30, 2014.
72 Azilect [package insert]. Kansas City, MO; Teva Neuroscience; June 2014.
73 Etminan M, Samii A, Takkouche B, et al. Increased risk of somnolence with the new dopamine agonists in patients with Parkinson's disease: a meta-analysis of randomized controlled trials. Drug Saf. 2001; 24:863-8.
74 Mirapex [package insert]. Ridgefield, CT; Boehringer Ingelheim; March 2013.
75 Requip [package insert]. Research Triangle Park, NC; GlaxoSmithKline; April 2009.
76 Parlodel [package insert]. Suffern, NY; Novartis; January 2012.
77 Requip XL [package insert]. Research Triangle Park, NC; GlaxoSmithKline; December 2012.
78 Stalevo [package insert]. East Hanover, NJ; Novartis; July 2014.
79 Available at: http://www.fda.gov/Drugs/DrugSafety/ucm223060.htm. Accessed August 8, 2014.
80 Neupro [package insert]. Smyrna, GA; UCB, Inc.; April 2012.
81 Horizant [package insert]. Research Triangle Park, NC; GlaxoSmithKline; July 2013.
82 The American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2012;1-16. Available at: http://www.americangeriatrics.org/files/documents/beers/2012BeersCriteria_JAGS.pdf. Accessed August 8, 2014.
83 FDA Medwatch. Mirapex (pramipexole): drug safety communication – ongoing safety review, possible risk of heart failure. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm320054.htm. Accessed August 8, 2014.
84 Etminan M, Samii A, Takkouche B, et al. Increased risk of somnolence with the new dopamine agonists in patients with Parkinson's disease: a meta-analysis of randomized controlled trials. Drug Saf. 2001; 24:863-8.
85 Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm258819.htm. Accessed August 8, 2014.
86 Mirapex [package insert]. Ridgefield, CT; Boehringer Ingelheim; March 2013.
87 Requip [package insert]. Research Triangle Park, NC; GlaxoSmithKline; April 2009.
88 Requip XL [package insert]. Research Triangle Park, NC; GlaxoSmithKline; December 2012.
89 Horizant [package insert]. Research Triangle Park, NC; GlaxoSmithKline; July 2013.
90 Olanow CW, Watts RL, Koller WC, et al. An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. Neurology. 2001; 56(Suppl 5):S1-88.
91 Olanow CW, Watts RL, Koller WC, et al. An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. Neurology. 2001; 56(Suppl 5):S1-88.
92 Parlodel [package insert]. Suffern, NY; Novartis; January 2012.
93 Mirapex [package insert]. Ridgefield, CT; Boehringer Ingelheim; March 2013.
94 Mirapex ER [package insert]. Ridgefield, CT; Boehringer Ingelheim; May 2014.
95 Requip [package insert]. Research Triangle Park, NC; GlaxoSmithKline; May 2009.
96 Requip XL [package insert]. Research Triangle Park, NC; GlaxoSmithKline; December 2012.
97 Neupro [package insert]. Smyrna, GA; UCB, Inc.; April 2012.
98 Mirapex [package insert]. Ridgefield, CT; Boehringer Ingelheim; March 2013.
99 Mirapex [package insert]. Ridgefield, CT; Boehringer Ingelheim; March 2013.
100 Voon V, Hassan K, Zurkowski MD, et al. Prevalence of repetitive and reward-seeking behaviors in Parkinson disease. Neurology. 2006; 67:1254-7.
101 Voon V, Thomsen T, Miyasaki J, et al. Factors Associated with Dopaminergic Drug-Related Pathological Gambling in Parkinson Disease. Arch Neurol. 2007; 64:212-216.
102 Comtan [package insert]. East Hanover, NJ; Novartis; June 2014.
103 Tasmar [package insert]. Costa Mesa, CA; Valeant Pharmaceuticals; May 2013.
104 Olanow CW. Tolcapone and hepatotoxic effects. Tasmar Advisory Panel. Arch Neurol. 2000; 57:263-7.
105 Azilect [package insert]. Kansas City, MO; Teva Neuroscience; June 2014.
106 Selegiline (Eldepryl). Available at www.clinicalpharmacology.com. Accessed July 30, 2014.
107 Zelapar [package insert]. Costa Mesa, CA; Valeant Pharmaceuticals; February 2009.

108 Selegiline [package insert]. Toronto, Canada; Apotex. November 2003.
109 Available at: www.clinicalpharmacology.com. Accessed July 30, 2014.
110 Horizant [package insert], Research Triangle Park, NC; GlaxoSmithKline; July 2013.
111 Gabapentin enacarbil (Horizant) for restless legs syndrome. Med Lett Drugs Ther. 2011; 1372:70.
112 Available at: www.clinicalpharmacology.com. Accessed July 30, 2014.
113 Tasmar (package insert). Aliso Viejo, CA; Valeant Pharmaceuticals; May 2013.
114 Tasmar [package insert]. Costa Mesa, CA; Valeant Pharmaceuticals; May 2013.
115 Carbidopa; levodopa. Available at: www.clinicalpharmacology.com. Accessed July 30, 2014.
116 Benztropine (Cogentin). Available at: www.clinicalpharmacology.com. Accessed July 30, 2014.
117 Trihexyphenidyl (Artane). Available at: www.clinicalpharmacology.com. Accessed July 30, 2014.
118 Azilect [package insert]. Kansas City, MO; Teva Neuroscience; June 2014.
119 Etminan M, Samii A, Takkouche B, et al. Increased risk of somnolence with the new dopamine agonists in patients with Parkinson's disease: a meta-analysis of randomized controlled trials. Drug Saf. 2001; 24:863-8.
120 Mirapex [package insert]. Ridgefield, CT; Boehringer Ingelheim; March 2013.
121 Requip [package insert]. Research Triangle Park, NC; GlaxoSmithKline; April 2009.
122 Parlodel [package insert]. Suffern, NY; Novartis; January 2012.
123 Requip XL [package insert]. Research Triangle Park, NC; GlaxoSmithKline; December 2012.
124 Stalevo [package insert]. East Hanover, NJ; Novartis; July 2014.
125 Available at: http://www.fda.gov/Drugs/DrugSafety/ucm223060.htm. Accessed August 8, 2014.
126 Neupro [package insert]. Smyrna, GA; UCB, Inc; April 2012.
127 Horizant [package insert]. Research Triangle Park, NC; GlaxoSmithKline; July 2013.
128 Requip XL [package insert]. Research Triangle Park, NC; GlaxoSmithKline; December 2012.
129 Mirapex ER [package insert]. Ridgefield, CT; Boehringer Ingelheim; May 2014.
130 Gottwald MD, Bainbridge JL, Dowling GA, et al. New pharmacotherapy for Parkinson's disease. Ann Pharmacother. 1997; 31:1205-17.
131 Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med. 2001; 33(5):337-43.
132 Welsh M, McDermott MP, Holloway R, et al. Development and testing of the Parkinson's disease quality of life scale. Mov Disord. 2003; 18(6): 605-724.
133 Tourtellotte WW, Potvin AR, Syndulko K, et al. Parkinson's disease: Cogentin with Sinemet, a better response. Prog Neuropsychopharmacol Biol Psychiatry. 1982; 6:51-5.
134 Available at: www.ninds.nih.gov/disorders/parkinsons_disease/detail_parkinsons_disease.htm#105623159. Accessed August 8, 2014.
135 Koller WC, Hutton JT, Tolosa E, et al. Immediate-release and controlled-release carbidopa/levodopa in PD: A 5-year randomized multicenter study. Carbidopa/Levodopa Study Group. Neurology. 1999; 53:1012-9.
136 Stocchi F, Rascol O, Kieburtz K, et al. Initiating levodopa/carbidopa therapy with and without entacapone in early Parkinson disease: the STRIDE-PD study. Annals of Neurology. 2010; 68(1):18-27.
137 Katzenschlager R, Head J, Schrag A, et al. Fourteen-year final report of the randomized PDRG-UK trial comparing three initial treatments in PD. Neurology. 2008; 71(7):474-80.
138 Rascol O, Brooks DJ, Melamed E, et al. Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomised, double-blind, parallel-group trial. Lancet. 2005; 365(9463):947-54.
139 Olanow CE, Rascol O, Hauser R, et al; ADAGIO study investigators. A double-blind, delayed start trial of rasagiline in Parkinsons's disease. N Engl J Med. 2009; 361:1268-1278.
140 Holloway RG, Shoulson I, Fahn S, et al for the Parkinson Study Group. Pramipexole vs. levodopa as initial treatment for Parkinson disease: a 4-year randomized controlled trial. Arch Neurol. 2004; 61:1044-53.
141 Biglan KM, Holloway RG Jr, McDermott MP, et al. Parkinson Study Group CALM-PD Investigators. Risk factors for somnolence, edema, and hallucinations in early Parkinson disease. Neurology. 2007; 69(2):187-95.
142 Parkinson Study Group CALM Cohort Investigators. Long-term Effect of Initiating Prampipexole vs Levodopa in Early Parkinson Disease. Arch Neurol. 2009; 66(5):563-70.
143 Parkinson Study Group. Pramipexole in levodopa-treated Parkinson disease patients of African, Asian, and Hispanic heritage. Clin Neuropharmacol. 2007; 30(2):72-85.
144 Noyes K, Dick AW, Holloway RG, et al. Pramipexole versus levodopa in patients with early Parkinson's disease: effect on generic and disease-specific quality of life. Value Health. 2006; 9(1):28-38.
145 Rascol O, Brooks DJ, Korczyn AD, et al. 056 Study Group. Development of dyskinesias in a 5-year trial of ropinirole and L-dopa. Mov Disord. 2006; 21(11):1844-50.
146 Thomas A, Bonanni L, Di Iorio A, et al. End-of-dose deterioration in non ergolinic dopamine agonist monotherapy of Parkinson's disease. J Neurol. 2006; 253(12):1633-9.
147 Tompson D, Oliver-Willwong R. Pharmacokinetic and pharmacodynamic comparison of ropinirole 24-hour prolonged release and ropinirole immediate release in patients with Parkinson's disease. Clin Neuropharmacol. 2009; 32(3):140-8.
148 Mirapex ER [package insert]. Ridgefield, CT; Boehringer Ingelheim; May 2014.
149 Giladi N, Boroojerdi B, Korczyn A, et al. Rotigotine Transdermal Patch in Early Parkinson's Disease: A Randomized, Double-Blind, Controlled Study Versus Placebo and Ropinerole. Movement Disorders. 2007; 22:2398-2404.
150 Watts RL, Jankovic J, Waters C, et al. Randomized, blind, controlled trial of transdermal rotigotine in early Parkinson disease. Arch Neurology. 2007; 64:272-276
151 Elmer, L, Surmann E, Boroojerdi B, Jankovic J. Long-term safety and tolerability of rotigotine transdermal system in patients with early-stage idiopathic Parkinson's disease. A prospective, open-label extension study. Parkinsonism and Related Disorder. 2012; 1-6.
152 LeWitt P, Lyons K, Pahwa R, et al. Advanced Parkinson disease treated with rotigotine transdermal system. Neurology. 2007; 68:1262-1267.
153 Trenkwalder C, Kies B, FCNeurol, et al. Rotigotine Effects on Early Morning Motor Function and Sleep in Parkinson's Disease: A double-blind, randomized, placebo-controlled Study (RECOVER). Movement Disorders. 2011; 26:90-99.

154 Poewe W, Rascol O, Quinn N, et al. Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomized controlled trial. Lancet Neurol. 2007; 6:516-520.
155 The Entacapone to Tolcapone Switch Study Investigators. Entacapone to tolcapone switch: Multicenter double-blind, randomized, active-controlled trial in advanced Parkinson's disease. Mov Disord. 2007; 22(1):14-9.
156 Rascol O, Brooks DJ, Melamed E, et al. Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomized, double-blind, parallel-group trial. Lancet. 2005; 365:947-54.
157 Montplaisir J, Boucher S, Gosselin A, et al. Persistence of repetitive EEG arousals (K-alpha complexes) in RLS patients treated with L-DOPA. Sleep. 1996; 19:196-9.
158 Kaplan PW, Allen RP, Buchholz DW, et al. A double-blind, placebo-controlled study of the treatment of periodic limb movements in sleep using carbidopa/levodopa and propoxyphene. Sleep. 1993; 16:717-23.
159 Trenkwalder C, Stiasny K, Pollmacher T, et al. L-DOPA therapy of uremic and idiopathic restless legs syndrome: a double-blind crossover trial. Sleep. 1995; 18:681-8.
160 Akpinar S. Restless legs syndrome treatment with dopaminergic drugs. Clin Neuropharmacol. 1987; 10:69-79.
161 Walker SL, Fine A, Kryger MH. L-DOPA/carbidopa for nocturnal movement disorders in uremia. Sleep. 1996; 19:214-8.
162 Benes H, Kurella B, Kummer J, et al. Rapid onset of action of levodopa in restless legs syndrome: a double-blind, randomized, multicenter, crossover trial. Sleep. 1999; 22:1073-81.
163 Collado-Seidel V, Kazenwadel J, Wetter TC, et al. A controlled study of additional sr-Ldopa in L-dopa-responsive restless legs syndrome with late-night symptoms. Neurology. 1999; 52:285-90.
164 Littner MR, Kushida C, Anderson WM, et al. Practice Parameters for the Dopaminergic Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder. Sleep. 2004; 27:557-9.
165 Winkelman JW, Sethi KD, Kushida CA, et al. Efficacy and safety of pramipexole in restless legs syndrome. Neurology. 2006; 67:1034 -9.
166 Oertel WH, Stiasny-Kolster K, Bergtholdt B, et al. Efficacy of pramipexole in restless legs syndrome: a six-week, multicenter, randomized, double-blind study (effect-RLS study). Mov Disord. 2007; 22(2):213-9.
167 Ferini-Strambi L, Aarskog D, Partinen M, et al. Effect of pramipexole on RLS symptoms and sleep: a randomized, double-blind, placebo-controlled trial. Sleep Med. 2008; 9(8):874-81.
168 Partinen M, Hirvonen K, Jama L, et al. Efficacy and safety of pramipexole in idiopathic restless legs syndrome: a polysomnographic dose-finding study–the PRELUDE study. Sleep Med. 2006; 7(5):407-17.
169 Bogan RK, Fry JM, Schmidt MH, et al. Ropinirole in the treatment of patients with restless legs syndrome: a US-based randomized, double-blind, placebo-controlled clinical trial. Mayo Clin Proc. 2006; 81:17-27.
170 Allen R, Becker PM, Bogan R, et al. Ropinirole decreases periodic leg movements and improves sleep parameters in patients with restless legs syndrome. Sleep. 2004; 27:907-14.
171 Montplaisir J, Karrasch J, Haan J, et al. Ropinirole is effective in the long-term management of restless legs syndrome: a randomized controlled trial. Mov Disord. 2006; 21(10):1627-35.
172 Walters AS, Ondo WG, Dreykluft T, et al. Ropinirole is effective in the treatment of restless legs syndrome. TREAT RLS 2: a 12-week, double-blind, randomized, parallel-group, placebo-controlled study. Mov Disord. 2004; 19:1414-23.
173 Trenkwalder C, Heike B, Poewe W, et al. Efficacy of rotigotine for treatment of moderate-to-severe restless leg syndrome: a randomized, double-blind, placebo-controlled trial. Lancet Neurol 2008; 595-604.
174 Oertel W, Heike B, Garcia-Borreguero D, et al. Efficacy of rotigotine transdermal system in severe restless legs syndrome: A randomized, double-blind, placebo-controlled, six-week dose-finding trial in Europe. Sleep Medicine. 2008 (9):228-239.
175 Oertel W, Trenkwalder C, Benes H, et al. Long-term safety and efficacy of rotigotine transdermal patch for moderate-to-severe idiopathic restless legs syndrome: a 5-year open-label extension study. Lancet Neurol. 2011; 10(8):710-720.
176 Hening WA, Allen RP, Ondo WG, et al. Rotigotine Improves Restless Legs Syndrome: A 6-Month Randomized, Double-Blind, Placebo-Controlled Trial in the United States. Move Dis. 2010; 25(11):1675-83.
177 Lee DO, Ziman RB, Perkins AT, et al. A randomized, double-blind, placebo-controlled study to assess the efficacy and tolerability of gabapentin enacarbil in subjects with restless legs syndrome. J of Clin Sleep Medicine. 2011; 7(3);282-292C.
178 Kushida CA, Becker PM, Ellenbogen AL, et al. Randomized, double-blind, placebo-controlled study of XP13512/GSK1838262 in patients with RLS. Neurologly. 2009; 72(5):439-446.
179 Horizant [package insert], Research Triangle Park, NC; GlaxoSmithKline; July 2013.

